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HUMAN LABORATORY INFECTION WITH VENEZUELAN EQUINE ENCEPHALOMYELITIS VIRUS*

Report of Four Cases

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THE occurrence of human cases of encephalomyelitis due to laboratory infection with Venezuelan equine encephalomyelitis virus was reported for the first time by Casals et al.[1] and by Lennette and Koprowski[2] in 1943. The course of the disease described by these authors varied from patient to patient; mild, almost ambulatory cases paralleled severer ones in which involvement of the central nervous system was manifest.

Two fatal cases with subsequent isolation of Venezuelan equine virus from the brain tissue were subsequently recorded.[3, 4] One of these cases preceded[3] whereas the other occurred during[4] an epizootic caused by the same virus among horses and mules in Trinidad, British West Indies.[4, 5]

Finally, Gallia and Kubes,[6] examining the serums of laboratory workers at the Institute of Veterinary Research in Caracas, Venezuela, found high titers of neutralizing antibody against Venezuelan equine encephalomyelitis virus in 10 of 16 cases. In only 1 of the 10 subjects involved, however, were there clinical manifestations that could have been attributed to the virus infection.

The purpose of the present report is to describe 4 human cases of laboratory infection with the Venezuelan virus, in 2 of which, prior to infection, there had been no known direct contact with the virus. The clinical course of the infection varied from a relatively mild disease to a severe infection that gave cause for alarm.

EPIDEMIOLOGY

In the second half of January, 1945, a strain of Venezuelan equine encephalomyelitis virus was obtained from Dr. J. Casals, of the Rockefeller Institute for Medical Research, New York. The virus was inoculated into mice on January 22. On January 25 the mice became sick and were sacrificed. The brains of the animals were removed, and an infectious brain suspension was distributed into ampules and lyophilized.

These experiments were carried out in an animal house, situated approximately 300 yards from the main laboratory, where all subsequent work with the virus was performed. On January 30 a tube of the lyophilized preparation was rehydrated, and the contents inoculated into a lot of fifty eggs containing developing chick embryos. The majority of the embryos were found to be moribund on the afternoon of January 31, when the embryos were harvested. The infected embryos were homogenized in a Waring blendor and then immediately formolized to prepare a vaccine.

The inoculation and harvesting of the embryos was done in a small sterile room to which only the personnel working directly with the Venezuelan virus, consisting of a physician and two assistant technicians, had access.

The eggs from which the infected embryos had been removed were deposited in a pail to which a 5 per cent solution of lysol was immediately added. All glassware and instruments used in the work were placed in a covered enamelware container. Late in the afternoon of January 31 the pail and the enamelware container were removed to the adjacent main laboratory, where three other persons, not connected in any way with the experiments on the Venezuelan virus, were working. On February 1 the pail was removed by a laboratory janitor to a disposal place, and the enamelware pan, containing the infected glassware and instruments, was filled with water and brought to the boiling point and then removed to the laboratory kitchen by the two assistant technicians who, on that day, did not have any further contact with the virus. The physician who was in charge of the work was absent from the laboratory on February 1.

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The first two human infections (Cases 1 and 2) appeared on February 2 in the assistant technicians who had been closely connected with the work on the virus. The third (Case 3) appeared in the evening of the same day in a biochemist who had not worked with the virus but who had been present in the main laboratory when the work with the virus was performed in the adjacent sterile room. Finally, the fourth infection (Case 4) appeared during the night of February 2 in a serologist who had not even worked in the main laboratory room, adjacent to the sterile room in which the studies on Venezuelan equine encephalomyelitis were carried on. On one or two occasions daily, however, he had passed the main laboratory room to and from his laboratory. The almost simultaneous occurrence of infection in the 4 patients indicated the presence of a common source of infection. This was strongly suspected to be connected with the work done on the Venezuelan virus, since the virus was known to be highly infectious[2] and since the only person who worked directly with the virus and did not show any symptoms of disease was the physician in charge, who was known to be immune to Venezuelan virus as a result of a previous infection.[2]

Case Reports

Case 1. D. F., a 24-year-old assistant laboratory technician, reported that she awoke on February 2 with a general feeling of malaise.* A throbbing frontal headache set in, and she remained in bed the entire day. In the afternoon she developed generalized muscular pains, felt weak, had no appetite and spent a sleepless night in spite of the ingestion of "sleeping pills."

Her condition remained essentially the same during the next day except that, in addition, she complained of pharyngeal irritation. A physician discovered no unusual physical findings and diagnosed the illness as "grippe," although the patient did her best to convince him that she had "Japanese encephalitis." She ascribed this notion to the fact that shortly before the onset of the illness she had been vaccinated with a formalin-inactivated preparation of mouse-brain suspension infected with Japanese B encephalitis virus. The physician prescribed sedatives and sulfadiazine.

On February 4 the patient felt "somewhat better." The headache, pharyngeal irritation and muscular pains persisted but were of diminished intensity. She still had no appetite and complained of drowsiness, although she stated that she was able to sleep only after taking large doses of "sleeping pills."

On February 5 the patient felt much better. The pharyngeal irritation, muscular pains and drowsiness disappeared, but a slight frontal headache remained. She asserted that she still felt weak and had no appetite. It is assumed, however, that convalescence began on that date (February 5), for 3 days later the patient was symptom free except for weakness. She reported back to work on February 14, stating that she had been too weak to make the trip to the laboratory before that date.

Case 2. D. J. S., a 22-year-old assistant laboratory technician, was well until about 10 a.m. on February 2, when she suddenly developed malaise and generalized body aches. The face was hot and flushed, and the whole body felt warm. The temperature was 101.1°F. After a specimen of the blood had been taken, the patient left the laboratory and went home to bed. She felt extremely drowsy and developed an almost unbearable headache localized between the eyes. Generalized body aches persisted, and she developed mild photophobia. She had no appetite but slept the entire night. The next day her condition remained unchanged, and a physician made the diagnosis of "grippe" and prescribed sedatives and sulfadiazine. The appetite remained poor, and the patient was quite weak. On February 4 she awoke feeling much better, since all the symptoms, except the frontal headache, had diminished. On the following day she suffered a slight relapse and again felt feverish, the headache became more accentuated and the feeling of malaise returned. The symptoms subsided in the evening, however, and she spent a restful night. On February 6 she spent an afebrile day and had few complaints. She still felt weak, but her appetite was normal.

Recovery was uneventful, and the patient reported back to work on February 15.

Case 3. D. W. McK., a 34-year-old biochemist, developed the illness on February 2, when at about 7 p.m., he suddenly noticed that he felt more tired than usual. During dinner he was conscious of a "lightheaded feeling," and a throbbing frontal headache soon appeared that was accompanied by a bothersome pharyngeal irritation. The headache became progressively worse, and at about 10 o'clock he started to have paroxysms of chills that lasted almost uninterruptedly for 2 hours. He had profound mental depression and during the night was feverish and delirious; at 3 a.m. he vomited partially digested food stained with bile. On the following day his condition remained unchanged except that he complained of muscular pains chiefly localized in the calf muscles. He was seen by a physician, who prescribed penicillin by mouth and a cough syrup containing codeine. In the afternoon a specimen of blood and a throat washing were taken. The patient slept during the 2nd night, and the temperature declined in the afternoon of February 4. The headache became less intense, but muscle and joint pains and pharyngeal irritation persisted.

On February 5 a macular rash appeared over the abdomen, inguinal folds and buttocks. The rash disappeared on the next day, and it was subsequently discovered that the patient was apparently sensitive to codeine, the administration of which had presumably caused the rash. The intensity of the systemic symptoms declined gradually throughout February 5 and 6.

On February 7 he awoke without the previous symptoms but developed complete anosmia and ageusia that persisted for 2 weeks and disappeared spontaneously.

On February 12 the patient resumed work at the laboratory.

Case 4.† D. W., a 36-year-old serologist, awoke on February 3 at about 4 a.m. with a shaking chill. The temperature was 102.9°F. A throbbing ache appeared over the occiput and in both eyes, and he experienced generalized muscular and joint pains. During the following 8 hours the patient had three more shaking chills, and the headache became severe and predominantly frontal and retro-orbital. The muscle pains became localized in the lumbar region. Since the patient had been working with material containing living *Rickettsia orientalis* during the period immediately preceding the illness, the possibility of scrub typhus infection was suspected, and he was hospitalized about 7 hours after the onset of symptoms.

Physical examination disclosed a well developed and well nourished man who appeared acutely ill. The temperature was 103.5°F., and the pulse rate 106. No abnormalities except tachycardia and a fairly loud blowing systolic murmur between the sternum and the apex of the heart were discovered. The total white-cell count was 10,600. A blood sample was obtained from the patient for bacterial culture and inoculation of animals.

At 5 p.m. the patient was still acutely ill and uncomfortable, with a severe throbbing headache, photophobia and profuse sweating. The temperature was 101.3°F., and the pulse rate 110. In spite of the fact that the patient had no rash, his condition was tentatively diagnosed as scrub typhus fever, and medication with methylene blue‡ — 2.0 gm. per day — was started at 8:15 p.m. One hour after taking the first 0.5-gm.

*The description of this case presented certain difficulties because the patient was highly susceptible to suggestion.

†Reported through the courtesy of Dr. Walsh McDermott, of the Department of Medicine, Cornell University Medical College.

‡Medication with methylene blue was based on the work of Petersen and Fox,[7] who observed survival of mice infected with scrub typhus following treatment with the agent.

dose, the patient became nauseated and vomited some of the drug.

On February 4 the patient was definitely improved, although he was still uncomfortable with a headache, muscular pains and pain in the calves. The temperature at 9 a.m. was 99.3°F., and the pulse rate 102 per minute; the total white-cell count was 5500. After another 0.5-gm. dose of methylene blue, the patient vomited, and the dosage was cut down to 0.25 gm. every 3 hours. On this dosage he was still nauseated but did not vomit. He also received two doses of 0.3 gm. of codeine sulfate. At 9 p.m. the temperature was 101.1°F.

On the following day the patient continued to improve. The temperature at 8 a.m. was 99.1°F. The headache had virtually disappeared, and the muscular pains and backache were of diminished intensity. Methylene blue was continued (0.25 gm. every 3 hours), and nausea persisted.

On February 6 the patient's condition had further improved. The temperature was 99.9°F. at 7 a.m. Since the results of the inoculation of the patient's blood into animals indicated that the diagnosis of scrub typhus fever was not probable, the administration of methylene blue was discontinued.

On the morning of February 7 the temperature was still 99.9°F. Examination of the urine revealed red cells and 15 to 20 white cells per high-power field in the sediment. This was considered to indicate cystitis or urethritis, possibly provoked by the ingestion of methylene blue.

During the next few days the patient's condition, except for a slight headache, remained essentially normal. The temperature averaged 100.4°F., and the white-cell count between 6200 and 8000.

On February 14 the severe headache recurred during the afternoon. The white-cell count was 14,000, but the patient was still almost afebrile. Lumbar puncture yielded a crystal-clear fluid. No bacterial organism was cultivated from the spinal fluid, and a complete laboratory analysis yielded practically negative results. Red cells were still present in the urine, although in diminished numbers. During the next day the patient's condition was practically normal except for a feeling of weakness and dizziness on standing. These symptoms gradually disappeared, and the patient was discharged from the hospital on February 23.

After discharge, recovery was uneventful, and the patient reported back to work on March 1.

Isolation of the Virus

No blood was obtained from the patient in Case 1 during the illness. Blood was obtained on the first day of the illnesses in Cases 2 and 4, and on the second day in Case 3.

Each specimen of serum was injected intracerebrally in amounts of 0.03 cc. into 6 albino Swiss mice twenty-one to twenty-eight days of age. All the inoculated mice were either sick or dead forty-eight hours after inoculation, and the survivors were sacrificed. The brains were removed, and a suspension was prepared according to a technic described elsewhere.[2] The bacteriologically sterile suspensions were then distributed in ampules, lyophilized and stored for five months at 4°C.

In addition, a throat washing obtained from the patient in Case 3 on the second day of the illness was inoculated intranasally in 0.05-cc. amounts into 10 mice. The majority of the mice were sick on the sixth day after inoculation. The sick mice were sacrificed, and since the lungs were normal on gross examination, the brains were removed and dealt with as mentioned above.

Five months later an ampule of each of the four strains was rehydrated with physiologic saline solution, and the contents were inoculated intracerebrally into mice. Forty-eight hours later, when the mice were moribund, the brains were removed and a 10 per cent suspension by weight was prepared in a TenBroeck grinder. The suspensions were centrifuged for fifteen minutes at 1500 r.p.m. in an International Size 1 machine equipped with an angle head, and the resulting supernatants were filtered through a Seitz EK pad, through which 20 cc. of normal rabbit serum and saline solution had previously been passed.

Serial tenfold dilutions of the four filtrates were made and tested for infectivity by the inoculation of albino Swiss mice, eighty to one hundred and twenty days old, with 0.03 cc. each by the intracerebral and intraperitoneal routes, respectively.

Rabbits, 1.4 to 2.3 kilograms in weight, were also injected with the filtrates, 2 animals being used for each of the 10^{-5} and 10^{-6} dilutions. All rabbits were injected by the intra-abdominal route with 1.0 cc. of the material.

The LD_{50}* titers of the four filtrates in mice varied between $10^{-8.5}$ and $10^{-9.5}$ by the intracerebral route and between $10^{-7.0}$ and $10^{-8.2}$ by the intraperitoneal route (Table 1). Thus, with the exception of Case 2, the intraperitoneal LD_{50} titer was only one log lower than the intracerebral. These results indicated that the causative agent readily passed the Seitz filter, and that it was of high invasive power for adult mice inoculated by the parenteral route.

The results of inoculation in rabbits (Fig. 1) further confirmed the highly invasive power of this filterable pathogen. All the animals reacted with fever and succumbed after a fulminant course of disease, with manifestations of marked cerebral involvement such as tremors, ataxia, clonic convulsions and paralysis; the rabbits died seventy-two to two hundred and sixteen hours after inoculation.

After the experiments had been concluded it became clear that the causative agent was a virus of neurotropic properties and of lethal action for adult mice(eighty to one hundred and twenty days old) and for rabbits, even when inoculated in a high dilution by the parenteral route. The Venezuelan equine encephalomyelitis virus seemed to correspond most closely to these characteristic properties,[2] and an attempt was therefore made for further identification.

Identification of the Virus

Neutralization tests were performed with the four infectious agents recovered from Cases 2, 3 and 4 and with serum from a rabbit that was known to be immune to Venezuelan equine encephalomyelitis. Normal and immune serums of the same animal were used in each case. The same rabbit serums had been used in previous experiments for identification of human strains of Venezuelan virus.[2] The technic of neutralization test followed exactly that previously described,[2] except that adult mice eighty to one

*LD_{50} represents the dilution of virus of which 0.03 cc. will kill 50 per cent of the mice within the test period.

hundred and twenty days of age, inoculated by the intraperitoneal route with 0.05 cc. of the respective virus dilution, were used throughout the study. Five mice were injected with each dilution. The test, with the agent recovered from Case 4, was done in duplicate, the second test being performed by Dr. J. Casals, of the Rockefeller Institute for Medical Research, on guinea pigs inoculated by the intra-abdominal route with mixtures of virus and immune serum.

Table 2 shows the results of the test. The immune rabbit serum that had previously been tested for specificity[2] showed a high neutralizing capacity for all four human strains. The guinea-pig test confirmed these findings, from which it may be deducted that the infectious agent was identical with the virus of Venezuelan equine encephalomyelitis virus.

TABLE 1. *Pathogenicity for Adult Mice of the Filterable Agent.*

CASE NO.	SOURCE OF VIRUS	ROUTE OF INOCULATION	MORTALITY RATIO WITH VIRUS DILUTIONS						LD50 TITER OF VIRUS
			10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}	
2	Serum	Intraperitoneal	5:5	3:4	2:5	2:5	0:5	0:5	$10^{-7.0}$
		Intracerebral	—	—	5:5	5:5	5:5	0:5	$10^{-9.5}$
3	Throat washing	Intraperitoneal	5:5	5:5	4:5	1:5	0:5	0:5	$10^{-7.5}$
		Intracerebral	—	—	4:4	5:5	1:5	0:5	$10^{-8.5}$
	Serum	Intraperitoneal	5:5	5:5	5:5	3:5	0:5	0:5	$10^{-8.2}$
		Intracerebral	—	—	5:5	5:5	1:5	2:5	$10^{-8.9}$
4	Serum	Intraperitoneal	5:5	4:4	3:4	1:5	1:4	0:5	$10^{-7.6}$
		Intracerebral	—	—	5:5	5:5	1:4	0:5	$10^{-8.7}$

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TABLE 2. *Results of Neutralization Tests with Human Viruses and Venezuelan Equine Encephalomyelitis Immune Serums in Adult Mice Inoculated by the Intra-abdominal Route.*

CASE NO.	SOURCE OF VIRUS	RABBIT SERUM	MORTALITY RATIO WITH SERUM AND VIRUS DILUTIONS										LD50 TITER OF VIRUS	LD50 DOSES OF VIRUS NEUTRALIZED
			10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}		
2	Serum	Normal	—	—	—	—	—	—	4:4	0:5	0:5	0:5	$10^{-7.5}$	
		Immune	4:5	3:5	0:5	0:4	0:5	0:5	0:5	—	—	—	$10^{-2.0}$	316,000
3	Throat washing	Normal	—	—	—	—	—	4:5	4:5	2:5	0:5	0:5	$10^{-7.4}$	
		Immune	4:5	2:5	0:5	0:5	0:5	0:5	—	—	—	—	$10^{-1.7}$	501,200
	Serum	Normal	—	—	—	—	—	5:5	4:5	3:5	1:5	0:5	$10^{-8.2}$	
		Immune	4:5	3:5	1:5	0:5	0:4	0:5	—	—	—	—	$10^{-2.2}$	1,000,000
4	Serum	Normal	—	—	—	—	—	5:5	5:5	4:5	0:5	0:5	$10^{-8.4}$	
		Immune	0:5	0:5	2:5	0:5	0:5	0:5	—	—	—	—	$10^{-1.0}$	25,120,000
	Serum	Normal*	—	—	4:4	4:4	4:4	4:4	4:4	4:4	—	—	$10^{-8.0}$	
		Immune*	—	0:4	0:4	0:4	0:4	0:4	—	—	—	—	$10^{-2.0}$	1,000,000

*Test performed with normal and immune guinea-pig serums by Dr. J. Casals, of the Rockefeller Institute for Medical Research. Guinea pigs instead of mice were used in the neutralization test.

APPEARANCE OF NEUTRALIZING ANTIBODIES

Blood was obtained from the patients in Cases 1, 2 and 3 at intervals of nineteen, nineteen and eighteen days, respectively, after the onset of symptoms. Blood was obtained from the patient in Case 4 on the thirty-fourth day after the onset of symptoms. These convalescent-phase serums were compared for neutralizing capacity with acute-phase blood specimens obtained from the patients in Cases 2, 3 and 4 on the first and second days of illness. To eliminate the presence of living virus from the acute-phase serums, the samples were submitted to inactivation for two hours at 56°C. and were used only after a safety test, performed in 6 mice observed for twenty-one days, had indicated the absence of living viruses from the specimen.

A strain of Venezuelan equine encephalomyelitis virus, obtained from Dr. Casals, was used as source in the neutralization test. The procedure of the test followed that described above.

The results of the test are presented in Table 3. The titer of the virus in the presence of acute-phase serums ranged from $10^{-7.6}$ to $10^{-8.2}$. In the presence of convalescent serums the LD_{50} titer of the virus was $10^{-1.0}$ or lower in Cases 2, 3 and 4 and $10^{-1.8}$ in Case 1. Thus, even in Case 1, in which no serum

sample obtained during the acute phase of the disease was available for comparison, it may safely be assumed that the patient, on February 20, was immune to the Venezuelan equine encephalomyelitis virus.

The development of antibodies in patients during their convalescence in concentrations neutralizing this laboratory. In 1938 the V-1938[8] strain of the virus was brought, for the first time, from Venezuela to the Lederle Laboratories and worked with for a period of about two years.[9] Although no signs of infection were observed among persons working with the virus at that time, it seemed to be of interest to examine the serums of those connected

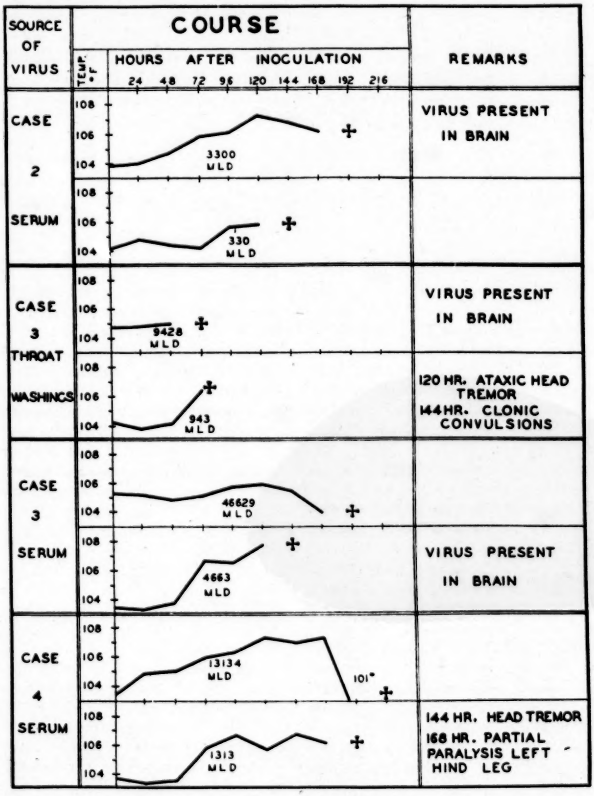

FIGURE 1.

130,000 or more minimal lethal doses of the Venezuelan virus is additional evidence that the human infections were due to this agent.

RESULTS OF NEUTRALIZATION TESTS IN PERSONS PREVIOUSLY EXPOSED TO VIRUS

The present infection was not the first occasion on which the Venezuelan virus has been brought to with the work for the presence of neutralizing antibodies directed against the Venezuelan virus. Blood was obtained from 3 of these persons (W. T., J. M. and J. K.) who were still working in the Laboratory and from another (H. R. C.), who had worked on the isolation of the virus from Case 4 of the present series. Blood was also obtained from 2 persons (M. P. and J. B.) who had been working in the

same room as the patient in Case 3 and who, although not in direct contact with the virus, had become sick with symptoms consisting of fever, headache and muscular pains almost simultaneously with the positively diagnosed cases described above. As a positive control of the test, a serum sample was obtained from one of us (H. K.) who had had Venezuelan equine encephalomyelitis in July, 1943.[2]

The technic of the test was the same as that described above.

The results are shown in Table 4. It will be observed that the titer of the virus, in the presence of immune serum of H.K., was lower than $10^{-3.0}$ whereas in the presence of serums obtained from other persons, the titer ranged from $10^{-7.0}$ to $10^{-8.5}$ — the usual titration end point of the virus in the absence of neutralizing antibodies.[10]

It may be assumed that the sickness of M. P. and J. B. was purely coincidental and that H. R. C., in spite of a recent direct contact with the Venezuelan virus, did not develop humoral immunity directed against this virus. Also, none of the persons (W. T., J. M. and J. K.) who had worked with the virus in 1938–1940 showed demonstrable specific antibodies in the blood, either because they had not become infected or because the amount of neutralizing antibodies in the blood had decreased below a detectable level.

Discussion

As mentioned above the Venezuelan virus was handled in this laboratory on only two occasions before it became the cause of human infections. On the first occasion, the work was carried out in the animal house to which 2 patients (Cases 3 and 4) did not have access at that time. Thus, it seems probable that these patients, as well as the other 2, became infected when the virus was handled in the main laboratory — that is, sometime between January 30, when a tube of lyophilized material was opened for inoculation of eggs, and February 1, when the eggshells and glassware and instruments used for harvesting of the chick embryos were disposed of. This would bring the incubation time of the disease in human beings up to three or four days, which is not improbable when compared with previous findings.[2]

The puzzling feature of the present report lies, however, in the fact that 2 patients became infected without having had any direct contact with

Table 3. *Results of Neutralization Test with Venezuelan Equine Encephalomyelitis Virus and Human Serums in Adult Mice Inoculated by the Intra-abdominal Route.*

Case No.	Interval after Infection	Mortality Ratio with Serum and Virus Dilutions										LD_{50} Titer of Virus	LD_{50} Doses of Virus Neutralized
	days	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}		
1	19	2:5	3:5	1:5	0:5	0:5	0:5	—	—	—	—	$10^{-1.8}$	?
2	1	—	—	—	—	5:5	5:5	5:5	2:5	0:5	0:5	$10^{-7.0}$	
	19	0:5	0:5	2:5	1:5	0:5	0:5	—	—	—	—	$10^{-1.0}$	7,943,000
3	1	—	—	—	—	5:5	5:5	4:5	1:5	1:5	0:5	$10^{-7.6}$	
	18	1:5	0:5	0:5	0:5	0:5	0:5	—	—	—	—	$10^{-1.0}$	3,981,000
4	3	—	—	5:5	5:5	5:5	5:5	5:5	3:5	0:5	0:5	$10^{-8.2}$	
	34	2:4	0:4	0:5	0:5	0:5	0:5	—	—	—	—	$10^{-1.0}$	15,850,000

Table 4. *Results of Neutralization Test with Venezuelan Equine Encephalomyelitis Virus and Serums of Persons Who Had Contact with Virus.*

Subject	Date of Withdrawal of Blood	Type of Work	Illness	Mortality Ratio of Adult Mice with Serum and Virus Dilutions								LD_{50} Titer of Virus
				10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}	
M. P.	2/21/45	Worked in the same room as Cases 1, 2 and 3	Yes	5:5	5:5	5:5	5:5	3:4	1:5	0:5	0:5	$10^{-7.6}$
J. B.	2/19/45	Worked in the same room as Cases 1, 2 and 3	Yes	5:5	5:5	5:5	5:5	2:5	1:4	0:5	0:5	$10^{-7.0}$
H. R. C.	7/30/45	Laboratory work connected with isolation of virus from Case 4	No	—	—	—	5:5	5:5	3:5	2:5	0:5	$10^{-8.5}$
W. T.	5/24/45	Laboratory work connected with isolation of virus from Case 4	No	—	—	—	5:5	4:5	4:5	1:5	0:5	$10^{-8.4}$
J. M.	5/24/45	Animal caretaker	No	4:4	5:5	5:5	5:5	3:5	0:5	0:5	0:5	$10^{-7.2}$
J. K.	5/24/45	Animal caretaker	No	5:5	5:5	5:5	5:5	3:5	1:5	1:5	0:5	$10^{-7.8}$
H. K.	7/16/45	Positive control (laboratory infection in July, 1943)	Yes	0:5	0:5	0:5	0:5	—	—	—	—	$10^{-3.0}$

the virus. Moreover, as mentioned above, 1 of the patients (Case 4) did not even work in the same laboratory room in which work with the Venezuelan virus was carried on. Between January 30 and February 1 the work with Venezuelan virus was carried on in fertile eggs only, so that the latter must be considered the source of the infection in human beings. In view of what has been stated above, contact infection seemed to be out of the question, leaving inhalation of infectious material as the most probable route of infection. The type of infectious material that may have been inhaled by all 4 patients cannot be determined. One may speculate whether or not a small amount of the embryonic suspension spilled during blending, dried in the air and subsequently was inhaled by the patients, or whether some of the infected eggshells were crushed outside the containers and the resulting dust inhaled by the patients. Whatever the true fact may be, all speculations remain within broad limits of probability.

Nothing characteristic was observed about the course of the disease, which was similar in its signs and symptoms to that described by other authors.[1, 2] Fever, body aches and pains and a rather persistent and severe headache were common to all cases. Again, as described earlier,[2] 3 of the patients were believed to have had attacks of "grippe," the fourth being properly diagnosed only because of the patient's hospitalization.

Marked differences in the severity of the illness were also observed in the present series. Cases 1 and 2 were the least severe, whereas Case 4 was so severe as to give cause for alarm and, because of its severity and its period of remission, closely resembled Case 7 of the previous report.[2] In all the present cases, the course of the disease seemed to be severer than that described by Casals and his associates.[1]

Since the cases described above increased the number of cases of human infections reported in the literature as due to Venezuelan virus to 26, all observations related to that infection in human beings were tabulated (Table 5). It may be observed that of the 26 cases reported, 12 cases were diagnosed by direct isolation of the virus, whereas the remaining 14 cases were diagnosed on the basis of the appearance of antibodies in the blood of the subjects. As further shown in Table 5, only 2 cases — those described by Randall and Mills[3] and Gilyard[4] — occurred naturally, and they have been the only fatal cases reported so far. Of the remaining 24 cases, 14 were definitely due to laboratory infection, whereas the remaining 10 cases, reported by Gallia and Kubes,[6] were attributed to infections of probable laboratory origin, although since the respective subjects lived in Venezuela, there remains the possibility of an inapparent natural infection. In the entire series of 26 cases, besides the 2 fatal ones, 2 patients showed symptoms that were regarded as severe, 13 had mild symptoms and 9 had no symptoms, although the serums neutralized the Venezuelan virus.

TABLE 5. *Summary of Human Cases of Infection Due to Venezuelan Equine Encephalomyelitis Virus.*

SERIES	TOTAL NO. OF CASES	CASES WITHOUT SYMPTOMS	CASES WITH MILD SYMPTOMS	CASES WITH SEVERE SYMPTOMS	FATAL CASES	CASES WITH VIRUS ISOLATED FROM BLOOD	CASES WITH VIRUS ISOLATED FROM THROAT WASHING	CASES WITH VIRUS ISOLATED FROM BRAIN TISSUE	CASES WITH NEUTRALIZING ANTIBODIES IN CONVALESCENT SERUMS
Casals, Curnen and Thomas[1]	2		2			1	1		2
Lennette and Koprowski[2]	8		7	1		6	1		8
Randall and Mills[3] and Gilyard[4]	2				2			2	
Gallia and Kubes[6]	10	9	1						10
Koprowski and Cox	4		3	1		3	1		4
Totals	26	9	13	2	2	10	3	2	24

The facts that the only 2 fatal cases of Venezuelan encephalomyelitis occurred during an epizootic in Trinidad[3, 4] and that no known accidents were associated with the laboratory infections raise the question whether the relatively low infectiousness of the Venezuelan virus, observed in the latter cases, was related to the unnatural intranasal spread of the infection.* The human infections that occurred during the epizootic were, in all probability, caused by the bite of an infected mosquito, and the intracapillary route of infection may have resulted in a much more fulminant spread of the infection, ending in the death of the patients. On the other hand, the lack of reports of fatal human cases occurring among the inhabitants of Venezuela residing in regions where the virus is enzootic must be considered.

The invasive power of Venezuelan equine encephalomyelitis virus for man is high, and yet its virulence for man apparently remains comparatively low. The report of 2 fatal cases,[4] however, and the ease with which the virus causes laboratory infection indicate the caution that must be exercised in working with the pathogen.

*Further evidence for the intranasal route of infection is suggested by the fact that all attempts to isolate the virus from throat washings (Table 5) were successful.

Summary

Four cases of human infection with Venezuelan equine encephalomyelitis virus are reported. All were due to infection acquired in the laboratory. The virus was isolated from the circulating blood in 3 cases and from the throat washings in 1.

The diagnosis in these 3 cases as well as that in another was further substantiated by the appearance of specific neutralizing antibodies in the convalescent serums. These findings are discussed in the light of previous reports of human infection due to Venezuelan equine encephalomyelitis virus.

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A SURVEY OF THE FIRST THREE MONTHS OF OPERATION OF A VETERANS ADMINISTRATION MENTAL-HYGIENE CLINIC

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SINCE the Mental Hygiene Clinic of the Veterans Administration began operation in Boston on March 18, 1946, a number of questions have been asked concerning the management of patients, the therapeutic goals, the types of patients who present themselves for treatment, the results and so forth. Although it is too early to permit an adequate reply to all the inquiries, a survey of the first three months' activities may clarify somewhat the work and aims of the clinic.

Since its opening the clinic has grown steadily both in patient load and in staff, although no attempt has been made to publicize its existence. At the time of writing further expansion has been stopped by lack of sufficient space for treatment rooms. At present the clinic is housed in a wing of the West Roxbury Veterans Hospital, which it fills to overflowing. On completion of more spacious quarters, an increase of more than twice the present number of patients treated will immediately be possible.

The staff consists of three full-time psychiatrists, four part-time psychiatric consultants, three full-time psychologists, five full-time psychiatric social workers and an office force of appropriate size. The move to larger quarters will permit the staff to be augmented immediately by four psychiatrists, a psychologist and three social workers. The eventual size of the staff can only be guessed at, since its further increase will depend entirely on the number of patients.

All patients referred to the clinic from any source are accepted on a trial basis without preliminary screening. This is admittedly a generous admission policy, but in the initial stages of operation, it provides the only method of determining the types of patients that can be referred to a mental-hygiene clinic.

A broad base for referrals is being obtained, practically every community organization with which a veteran can be expected to make contact being represented. It is not surprising that by far the majority of patients are referred by some division of the Veterans Administration, but it is gratifying to note that of 228 patients, 19 were self-referred and 15 were referred by private physicians (Table 1).

Table 1. *Patients Referred from Various Sources.*

Source	No. of Patients
Medical Outpatient Department, Veterans Administration	80
Social Service Department, Veterans Administration	54
Self	19
Harvard Guidance Clinic	16
West Roxbury Veterans Hospital	15
Outside physicians	15
Vocational Rehabilitation Division, Veterans Administration	7
Contact Division, Veterans Administration	4
Veterans Service Center	4
Jewish War Veterans	4
Bedford Veterans Hospital	2
Jewish Family Society	2
Outside hospitals	2
Psychiatric clinic	1
Red Cross	1
Civil Service Commission	1
Clergyman	1
Total	228

Such an admission policy may be expected to give the clinic a high percentage of cases that will eventually prove to be therapeutic failures, but it is regarded as preferable at our stage of development

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not to have any predetermined diagnostic or other criteria for refusing new applicants for psychiatric assistance. Several factors have dictated this decision. In the first place, it has been the experience of military psychiatrists that patients who in civilian practice would be considered poor material for treatment respond to psychotherapy. Secondly, it is believed that this clinic should take the lead in the development of new therapeutic devices and technics of potential benefit in the management of patients hitherto considered resistant or unamenable to psychotherapy. A final reason for accepting all types of patients was that this practice keeps the clinic from becoming too one-sided and makes available a large and varied group of patients for teaching purposes.

So far as the legal aspects of this policy are concerned, eligibility for treatment has been established by Veterans Administration Circular No. 26, which, in effect, gives authority to the chief medical officer to determine whether or not a patient is eligible for psychiatric care. This permits immediate psychiatric care of veterans with service-connected disabilities, prior to completion of adjudication of their claims. A great advantage is that the policy avoids overstress of symptoms in the hope of receiving treatment. The veteran is not made to believe that he must exhibit extreme and dramatic evidences of his illness to be treated. The clinic is thus enabled to do prophylactic work, instead of limiting itself to patients who had already suffered symptoms and had been hospitalized for them while in military service.

Despite this "open-door" policy, the great majority of patients fall into the general grouping of psychoneurotic disorders, only 15 of a total of 228 cases being classed as character and behavior disorders that are generally not amenable to treatment (Table 2). The high percentage of anxiety reactions agrees with the general experience of clinics and psychiatrists treating veterans.

Since our methods of managing patients are rather different from those in use in other mental-hygiene clinics, a short description of the procedures is of interest. On referral the patient is immediately given an appointment for the orientation class. Orientation sessions are held three times a week, and thus the initial contact with the clinic staff need never be delayed more than twenty-four hours. The orientation session, which is conducted by a psychologist and lasts an hour, is designed to answer the veteran's questions about clinic procedure and rules, methods of treatment, what he can expect to be done *for* him and what the clinic will expect *from* him. An attempt is also made in this first session to relieve some of the anxiety about the label "psychoneurosis" and to give the patient a rational and acceptable, although superficial, explanation for some of his symptoms.

After orientation, a complete history is obtained by a social worker — this usually requires two appointments and may extend to three or four in complicated or retarded cases. Such an extended period with the social worker has proved to be extremely valuable in the management of treatment. Not only can the treatment be speeded up because the psychiatrist has available a complete case history before he sees the patient but also the interview with the social worker serves as superficial psychotherapy in itself. The patient is forced into a biographical orientation that prepares him for more searching therapy and frequently results in some reorientation toward his complaints before the initial contact with the psychiatrist. Furthermore, these interviews serve as a screening device for patients who are so unprepared for psychotherapy that they cannot even co-operate in the giving of biographical information at the conscious level.

TABLE 2. *Diagnoses.*

DIAGNOSIS		NO. OF PATIENTS
Transient personality reaction:		
Acute situational maladjustment		3
Psychoneurotic disorders:		133
Anxiety reaction	91	
Phobic reaction	2	
Conversion reaction	12	
Somatization reaction	5	
Obsessive-compulsive reaction	3	
Hypochondriacal reaction	2	
Neurotic depressive reaction	14	
Type undetermined	4	
Character and behavior disorders:		15
Immaturity reaction	7	
Pathological behavior reaction	5	
Pathological personality reaction	2	
Type undetermined	1	
Psychoses without known organic etiology:		
Schizophrenic disorders		5
Psychoses with associated structural changes		3
Gastrointestinal disease		3
Diagnosis deferred		66
Total		228

After the history has been taken the patient sees a psychiatrist for a survey, at which time the tentative diagnosis, prognosis and program of treatment are determined.

Treatment may take the form of individual psychotherapy in addition to environmental manipulations, individual psychotherapy, individual psychotherapy with Pentothal Sodium as an adjuvant, hypnotherapy or group therapy. The type of therapy depends solely on the psychiatrist's judgment of what will benefit the patient most, and the original program may be modified several times according to the patient's progress and responsiveness.

Since the great majority of patients respond reasonably well to individual psychotherapy with occasional sessions of Pentothal or hypnosis, this is the most frequently used method of treatment. Environmental manipulation is seldom utilized because of our deliberate policy of treating the patient

to as great an extent as possible exactly as if he were being treated by a psychiatrist in private practice. As a matter of policy, fifty hours of treatment has been set as the maximum, and it is our hope to render patients comfortable and symptom free in much less time.

Although it is too early for any definitive statistics on length of treatment, after three months' work, the Clinic has begun to build up a small but not inconsequential number of patients who have been treated for ten, fifteen and even twenty-eight hours (Table 3). Only a longer period will tell how

TABLE 3. *Hours of Treatment Given to All Patients on June 30, 1946.*

Hours of Treatment	No. of Patients
1	1
2	10
3	14
4	10
5	22
6	13
7	12
8	12
9	8
10	4
11	4
12	2
13	3
14	2
15	2
16	1
18	1
19	3
28	1

successful the treatment of such patients has been. These clinic "veterans" may have built up too great a dependence on the psychiatrist, although clinical judgment in these cases does not support this opinion. Rather, it seems that these men, who are being carried for longer periods, continue to come because they are gaining real — although limited — insight and increased skill in handling their interpersonal problems.

Group therapy is frankly being used as a socializing technic with patients diagnosed as character and behavior disorders who do not respond well to individual treatment. It is a psychiatric commonplace that psychopaths are resistant to uncovering and interpretation procedures because of a warped development that has resulted in improper or inadequate identification with parental authority images. We are giving such patients group therapy with the expectation of making therapeutic use of sibling relationships, which usually develop in such groups.

Groups of 6 to 8 patients are formed with a psychologist as group leader. Each group meets twice a week for an hour at a time for six weeks. The group leader is prepared with a set of twelve short lectures on topics designed to elicit group discussion of troublesome interpersonal problems. Although the lectures are educational in themselves and correct many frequent misapprehensions, they are not considered treatment in themselves but are regarded as providing a stimulus for an atmosphere in which therapy can take place through group stimulation, development of sibling relationships and identification and recognition by each patient that his problem is not unique and individual but that he suffers from frequent symptoms with which his fellow sufferers can help him.

Each session is opened by a short presentation, lasting ten or fifteen minutes, of a triple-barreled topic designed to correct misapprehensions, elicit discussion and encourage emotional ventilation. Group discussion of the subject is invited and stimulated, the group leader serving as moderator but remaining unobtrusive so long as the patients continue to discuss any potentially therapeutic topic. At the end of the hour the leader summarizes the discussion and relates it to the specific problems of the men in the group.

Since the major purpose of group therapy is to develop sibling relationships, if a patient fails to keep an appointment for group therapy, one of the other patients who lives in his neighborhood endeavors to find the reason for his absence and to persuade him to return. It has been the policy of the Clinic not to have any member of the staff follow up patients who have ceased keeping their appointments. To do so would introduce an authoritarian element that, we believe, would disturb the type of emotional climate that we have been endeavoring to build up in the Clinic situation.

Our group-therapy program is considered effective in several ways, in addition to the building up of the sibling relationships and identifications mentioned above. Relaxation from tension, ventilation of hostility and aggression and considerable catharsis take place. Some patients obtain sufficient insight to become amenable to individual therapy after completion of a course of group therapy; others respond adequately to a simultaneous combination of group and individual therapy, attending group sessions twice a week and seeing a therapist once. Thus, group therapy is employed not only as treatment per se but also as a preparation for, and an adjuvant to, individual treatment.

The results obtained are demonstrated in Table 4, which summarizes according to diagnosis the disposition of all cases in our files on June 30, 1946. Fifteen per cent of the total were either discharged or referred to other agencies for indicated treatment, 28 per cent voluntarily ceased keeping appointments, and 55 per cent were being carried in treatment status. All diagnoses were represented to about the expected extent in each group, and the small number of discharges is to be expected from the short life of the Clinic. Our records show that the patients discharged as "improved" had been given an average of six and a half hours of treatment, and those discharged as "unimproved," five and a half hours.

Since the 28 per cent of patients who voluntarily ceased treatment before they were discharged in a sense constituted failures, this group was surveyed as intensively as the records permitted. In both diagnosis and source of referral the patients were not distinguished from the remainder treated. We were struck with the fact that 25 per cent of the group ceased reporting to the Clinic before they had made *any* contact with a psychiatrist and that of the professional staff. Once a week a staff conference lasting an hour is held for psychiatrists and psychologists. At each meeting a member of the staff presents a case currently being treated. The dynamics behind the symptoms, the treatment program, the therapeutic technics and so forth are discussed and criticized by the entire staff. At these meetings, such considerations as problems of diagnostic nomenclature, sources and methods of

TABLE 4. *Dispositions of Patients as of June 30, 1946.*

DIAGNOSIS	PATIENTS DISCHARGED IMPROVED	PATIENTS DISCHARGED UNIMPROVED	PATIENTS FAILING TO KEEP APPOINTMENTS	PATIENTS REFERRED TO VETERANS ADMINISTRATION, PROVIDENCE, R.I.	PATIENTS REFERRED TO MASSACHUSETTS GENERAL HOSPITAL	PATIENTS REFERRED TO PSYCHIATRY CLINIC	PATIENTS ADMITTED TO HOSPITALS	PATIENTS BEING TREATED IN MENTAL-HYGIENE UNIT
Transient personality reaction:								
Acute situational maladjustment	1							2
Psychoneurotic disorder:								
Anxiety reaction	7	1	27	1		3	1	51
Conversion reaction	1		2					9
Obsessive-compulsive reaction	1							2
Neurotic depressive reaction	3		5		1	1		4
Somatization reaction			1					4
Hypochondriacal reaction			1					1
Headache, cause undetermined							1	
Phobic reaction								2
Type undetermined		1					1	1
Character and behavior disorder:								
Immaturity reaction	1*	1†	1					
Pathologic behavior reaction	1‡		3					1‡
Pathologic personality reaction			1					
Passive aggressive reaction								2
Aggressive reaction								2
Schizoid personality								1
Type undetermined			1					
Psychosis without known organic cause:								
Schizophrenic disorder			1				2	2
Epilepsy							1	2
Gastrointestinal disease					3			
Diagnosis deferred or undetermined			24		1			41
Totals	15	3	67	1	5	4	6	127

*With symptomatic habit reaction.
†With speech defect.
‡Inadequate depressed reaction.

an additional 30 per cent failed to return after the first treatment interview. After the third hour of treatment the rate of attrition dropped off steeply, only 16 per cent of patients being lost. These findings strongly suggest that the patients ceased treatment because they were disappointed to find that the staff possessed no magical serums or formulas by means of which all their problems could be quickly and painlessly solved. The discovery that psychiatric treatment may be an uncomfortable process was probably too much for them, and they decided that to endure their symptoms would be less disturbing than to face them. It is to be expected that most of these men will return to the Clinic when their symptoms become severer, and a few have already done so. A survey is being conducted by the Social Service Department to discover the specific reason for discontinuance in these 67 cases.

Questions have been asked about the staff-training program and therapeutic goals. A definite educational program has been set up for all members

referral and the relative efficacy of various methods are brought to the attention of the staff.

For the social workers on the staff and those assigned to the Out-Patient Department two weekly seminars of an hour and a half each are held. Although primarily designed for social workers, the seminars may be attended by other staff members who are free at the time. In these seminars clinic plans, methods and procedures, basic psychologic theory, the history of and the underlying dynamics involved in various anamnestic and therapeutic technics are discussed. Also, in each session, a complete case is discussed with emphasis on the dynamics and on the clues to dynamics that can be picked up during history taking.

A word about our therapeutic goals may be of interest. We are not deluding ourselves with the belief that a large proportion of patients will be cured in the relatively short period of treatment that has been set up as the maximum. Our experience, however, convinces us that an active therapeutic approach will enable us materially to improve the condition of a high percentage of

patients. Real, although limited, insight can be gained, elementary interpretations accepted and synthesized, anxiety reduced, and a program of living that involves a minimum of interpersonal conflicts adopted within the time limitations of the therapy provided in the clinic. Although the patient may not be completely well, he can be taught to recognize the sources of his difficulties and given technics for avoiding most of the larger collisions. Our aim, then, may be summarized by an analogy from the field of physical medicine: when we cannot cure the disease, we try to provide an adequate form of compensation. It is our hope that our compensated neurotic patients may, like compensated cardiac patients, lead successful and satisfying lives, although more restricted than those of normal persons.

Summary

A description is presented of the location, staff, admission policy, clinic procedures, staff training program, therapeutic goals, types of treatment given and results of the Veterans Administration Mental Hygiene Clinic in Boston at the close of its first three months of operation.

Individual psychotherapy is the method of choice, but group therapy plays an important role in the treatment program. The type of group therapy utilized is briefly described.

Analysis of the progress of 228 patients shows that approximately 15 per cent were discharged, that the treatment in 28 per cent had lapsed and that 55 per cent were undergoing active treatment.

CREEPING ERUPTION IN NEW ENGLAND*

A Report of Two Cases

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ONE of the cases of creeping eruption reported below was attributed to the dog hookworm, *Ancylostoma caninum*, and was actually acquired in Boston. Although frequent enough in tropical and subtropical countries, this infection has been reported only once before in New England, in a patient who became ill in Florida.[1] The clinic to which the patient in Case 1 reported would probably have been confounded by his skin lesion had he not brought with him a note from a physician in Louisiana who had made the proper diagnosis. The patient in Case 2 had previously suffered from creeping eruption, and the appearance of the lesion was known to his mother, so that the problem of initial diagnosis was not present. Since this peculiar lesion may occur oftener in New England, this report should aid in its immediate recognition.

CASE 1 (C. H. 308407). R. V., a 2½-year-old boy, was first seen on August 13, 1946, in the Medical Out-Patient Department of the Children's Hospital, because of a localized skin lesion. Accompanying him was a note from the Station Hospital at Camp Pope, Louisiana, stating that the patient had been treated on August 1 with ethyl chloride because of "hookworm infection of the left foot." The social and past histories were noncontributory.

The patient had been well until July 28, when he was living with his mother and father, a lieutenant in the Army, at Camp Pope. He had been permitted to play outdoors unrestrictedly and had frequently been observed playing without his shoes. On July 28 the mother first noted a large red papule on the left foot between the first and second toes. This was evidently pruritic and kept the patient awake at night. Two days later the lesion had become about 12 cm. long and described a circinate course over the dorsum of the foot. On August 1 the patient was seen at the camp hospital, and a diagnosis of "hookworm disease of the skin" was made. Local ethyl chloride therapy was instituted. Subsequently, a moderately severe slough resulted. Penicillin ointment was applied over the lesion, which healed without complications. On August 3 the family departed for Boston, where they took up residence with the maternal grandparents. Four days later the mother noted two new papules, one over the left tibia and one on the flexor surface of the right forearm. On August 12 the papules had changed to circinate lesions 2 to 3 cm. long. Pruritus again became troublesome, and the child was unable to sleep at night. Because of this, medical advice was sought.

Physical examination revealed an apparently well developed and well nourished child who was in no distress except for the itching skin lesions. On the left instep an area of new epidermis, 8 by 12 cm. in diameter, was visible. This was healing well. On the flexor surface of the left forearm and over the left tibia were single 4-cm. long, irregular, raised, serpentine lesions 2 mm. wide and surrounded by evidence of recent excoriation. Occasional vesicles, 2 mm. in diameter, were present on either side of the burrows. The rest of the physical examination was of no consequence. Since a consultation with the Department of Tropical Medicine, Harvard Medical School, could not be obtained until August 17 the mother was instructed to treat the lesions with calamine lotion in an attempt to control the itching, and to return for consultation.

On August 17 a new eruption had appeared on the left biceps within the previous 24 hours. This lesion was similar to those previously noted. Consultation confirmed the diagnosis of creeping eruption, and therapy with carbon dioxide snow was advised. Three days later examination of the blood disclosed a red-cell count of 3,800,000, with a hemoglobin of 74 per cent (10.5 gm.) and a white-cell count of 10,300, with 39 per cent neutrophils, 50 per cent lymphocytes, 3 per cent monocytes and 8 per cent eosinophils. Examination of the patient's stools on two occasions was negative for intestinal parasites.

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On August 23 the carbon dioxide snow was administered. A week later the child returned because of failure of the lesions on the right forearm and left leg to respond. The lesion on the right forearm was 4 cm. long, red, raised and circinated (Fig. 1). Freezing therapy was again instituted. When the patient was seen last on September 13, the eruption on the left leg was still present.

Case 2. R. C., a 5½-year-old boy, was first seen at the Department of Tropical Medicine, Harvard Medical School, on August 31, 1946. He had been referred by a physician because of a skin rash on the legs and arms.

The child had been without complaints until the middle of July, 1945. At that time, he was at home in Savannah, Georgia, where he frequently played in the yard without shoes or stockings. One evening when he came home his mother noticed raised red "bumps" on his forearms and legs. These apparently did not itch. In 24 hours the lesions began to progress and became extremely pruritic. The family physician made a diagnosis of "creeping eruption." Ethyl chloride was applied locally for about 1 minute to each lesion. This therapy was repeated almost every 4 days until October 1, when there were no more active burrows. The patient remained well until July, when, after he had played in a pit in which cats were known to have defecated about thirty new, red, raised bumps were noted on the arms and legs. These lesions apparently appeared within 4 hours after the child became infected. As before, the macules were nonpruritic until the elongation of the burrows was apparent. Thereafter, the child was annoyed by itching. About August 1 the family left Georgia for a visit to the grandparents in New Hampshire. Owing to the severe itching, a physician was called to see the child. Two weeks later a differential count revealed an eosinophil count of 40 per cent. Because of lack of familiarity with this form of skin disease the child was referred to the Harvard Department of Tropical Medicine.

Physical examination revealed about thirty irregularly serpiginous lesions on the arms and legs that showed some evidence of excoriation. The child was not febrile, and there was no other evidence of disease. A stool specimen obtained at that time revealed no intestinal parasites. Ethyl chloride therapy was again instituted, with almost immediate relief and eradication of most of the lesions.

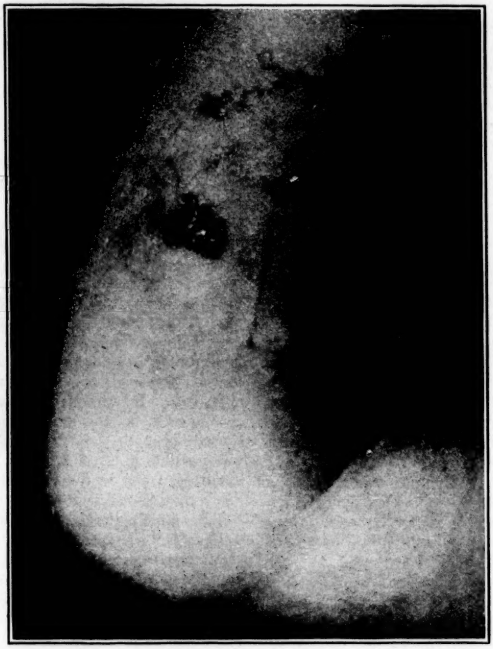

Figure 1. *Case 1.*

This photograph of the right forearm was taken on August 30. A central area of granulation tissue is present in the area that had received carbon dioxide-snow therapy one week previously. The burrow proximal to this had almost healed. The distal lesion appeared after therapy.

Creeping eruption caused by nonhuman hookworm larvae usually involves one or two species of cat and dog hookworms — *A. braziliense* and *A.*

caninum. Whereas both species are frequent intestinal parasites of both hosts, *A. braziliense* occurs oftener in cats and *A. caninum* occurs more frequently in dogs. Both are world wide in distribution; *A. braziliense*, which is widely established in tropical and subtropical countries, is not normally found in North America as far north as Baltimore.[2] Although *A. caninum* is likewise widely distributed throughout the warm countries, it differs from *A. braziliense* in that its range extends well into temperate climates. It is a frequent and important parasite of dogs in New England.

The first accurate knowledge of the life history of hookworms was gained from the experimental studies with *A. caninum* by Looss[3] in 1911. Eggs, which are the product of the adult male and female worms in the intestine, are deposited on the soil with the feces of the infected host. Development of the embryo is rapid, and hatching occurs in about twenty-four hours. The young hookworm larva, which feeds on bacteria in its environment, reaches its third stage of development — the infective stage — within about five days. Favorable temperature, moisture and type of soil are primary requisites for this development.[4, 5] Having reached the infective stage, the larva no longer feeds during its free existence; its main function is to carry the species to a new host. In moist soil it remains extended from the uppermost soil particles, singly or in large aggregates, within the immediate area of soil pollution.[6] When these infective larvae, which are markedly thermotropic, are transferred to the skin of warm-blooded animals, activity is greatly aroused, and almost immediately the larvae begin boring into the tissues. Once within the proper host, the infective larvae quickly leave the dermal tissues, enter the lymphatic vessels, and after a circuitous migration, arrive in the small intestine, where they become adult male and female worms.

When infective hookworm larvae invade the skin of a foreign or refractory host, they frequently fail to leave the dermal tissues, through which they burrow indefinitely, producing indurated, sinuous tunnels that progress at the rate of several millimeters to a few centimeters each day. Without intervention, such larvae may continue their migration for weeks or months. This behavior is characteristic of cat and dog hookworm larvae attempting to infect the human body.

A stinging, prickling sensation may be experienced at the time the larvae invade the skin. The first visible lesions — maculas and papules — usually appear after the second or third day of infection, tunnel formation beginning on or after the fourth day of infection. As the advancing end of the line progresses, the opposite end fades away.

Differences have been noted in experimental infections in the type of lesion caused by *A. braziliense* and *A. caninum*.[7] The lesions caused by the former are characteristically continuous with the points of entry of the larvae, whereas those of the latter may be discontinuous, apparently because these larvae penetrate the deeper tissues and later return to the surface of the skin at some distance from the point of entry. Marked variations have also been noted in different persons following experimental or accidental infection with a known species.[8] Therefore, it is not possible to make a specific diagnosis on the character of the lesion or to identify the species on larvae excised from a lesion. The most helpful definitive differential diagnostic method is the isolation of adult hookworms from the small intestine of the animal presumably responsible for the human infection. The diagnosis of *A. caninum* infection was made in Case 1 by means of this procedure.

The fact that new lesions in Case 1 appeared two weeks after the patient arrived in Boston clearly suggested that these last lesions had been acquired locally and that the source of infection was nearby. On questioning, it was learned that the family pet was a five-and-a-half-month-old cocker spaniel that had been acquired in Louisiana and had accompanied the family to Boston. A stool from the dog was examined on August 19 and found to be positive for hookworm eggs. On the request of the mother, the dog was sacrificed at the Angell Memorial Hospital. At autopsy, twenty-two male and thirty-four female *A. caninum* were removed from the small intestine. Since this dog appeared to be the only source of infection, it was concluded that the lesions in this patient were caused by that organism. No specific diagnosis was possible in Case 2. Since, however, cats, but not dogs, were on the premises in Savannah, it is likely that the causative agent was *A. braziliense*.

To complete the study of the patient in Case 1, soil samples were taken from around the house of the family to determine areas of soil infection. This house, typical of many in eastern cities, had a small enclosed back yard, which limited the excursions of both the boy and the dog. Most of the enclosure was so overgrown with bushes and tall grass that the boy's play yard was largely restricted to a small area under a rear porch and its steps, which was also the habitual place in which the dog defecated. Almost continuous rains since the arrival of the family in Boston rendered this particular spot ideal for the development of hookworm larvae.[4, 5] On completion of selection of soil samples, it was learned that the mother had flooded the area with boiling water the day the dog had been sacrificed. No hookworm larvae were found in any of the soil samples. Since no new lesions have been acquired, it appears that the use of boiling water had effectively destroyed any hookworm larvae in the area.

Despite the common occurrence of creeping eruption in certain parts of the world, *A. caninum* and *A. braziliense* seldom cause intestinal parasitism in

man. Two naturally acquired infections with the former are recorded from the Philippine Islands,[9] and a third infection has been reported in a boy in Texas.[7] It therefore appears that man is highly resistant to infection with *A. caninum* and that the infective larvae of this species seldom leave the dermal tissues, where they are effectively destroyed. *A. braziliense*, which is more successful as a human intestinal parasite, is a relatively frequent intestinal parasite of man throughout the Orient and is rare in the Amazon Valley, Brazil.[10] Only one such infection has been noted in the United States.[7] This occurred in the same boy in Texas, who was also infected with *A. caninum* and *Necator americanus*. Individual infections have always been light.

The relative frequency of human intestinal infection with *A. braziliense* in the Orient and its apparent absence in the Western Hemisphere have suggested a duality of types — that is, an oriental type, which has become better adapted to the human host, and an occidental type, which is merely in the first stage of adaptation. The fact that creeping eruption, the manifestation of host resistance, is common in the southeastern states, where human intestinal infection with this hookworm is virtually unknown, and the absence of creeping eruption and the rather frequent intestinal infections with *A. braziliense* in the Philippine Islands, as reported by Africa,[11] support the view that two distinct types of this species exist.

Creeping eruption is relatively rare among Negroes. Dove[7] reported that of 301 cases of creeping eruption at Jacksonville, Florida, only 5 (1.6 per cent) occurred in Negroes. There is also a marked racial difference in the incidence and intensity of hookworm infection (*N. americanus*). In endemic areas and when living under almost identical conditions of sanitation, economic status, occupation, soil, temperature and rainfall, the Whites characteristically have a heavy hookworm infection, whereas the Negroes have a light one.[12] There is no explanation of this fact, but it is believed to be due to a physiologic difference in the two races — namely, the much greater thickness of the epidermis of the Negro, which provides a natural barrier against infective hookworm larvae.

In view of the fact that *A. caninum* is a relatively frequent parasite of dogs in New England, the question arises concerning the reason for the rarity of creeping eruption in the human population. *A. caninum* occurs most frequently in New England kennels. The infection is rare in stray and vagrant dogs, but is a characteristic infection of puppies. Well nourished adult dogs are highly resistant to hookworms.[13] Puppyhood is of relatively short duration, and the hookworms acquired in a kennel are self-eliminated as the dog matures. Accurate data are not available, but it is highly probable that for most New England farm dogs and house pets harboring hookworms, the infections are light. The lack of a sufficient number of consecutive days with favorable temperature and moisture for larval growth of the parasite in New England soil, together with light hookworm infections in the dogs, does not permit the development of a heavy soil infection under most circumstances. Only in kennels and under unusual conditions, such as those in Case 2, are soil infections likely to become sufficiently heavy and concentrated to cause creeping eruption. The apparent absence of creeping eruption among kennel owners and workers in New England may be attributed to the wearing of footgear, which adequately protects the skin against immediate contact with hookworm larvae in the soil.

Thus far, the most satisfactory treatment for creeping eruption is local freezing, applied to the skin in the advancing area of the lesion. Either carbon dioxide snow or ethyl chloride spraying may be used.[14] Fuadin (antimony biscatechol disulfonate of sodium) has been tried with variable success.[15, 16] A yearly fecal examination of pet dogs and cats, with anthelmintic treatment to those found positive for hookworms, would provide a practical precautionary measure.

Summary

Two cases of creeping eruption are reported, one of which was certainly caused by *Ancylostoma caninum* of canine origin and was acquired in Boston. The second case, acquired in Georgia and observed in Boston, was probably caused by *Ancylostoma braziliense*. A review of the literature failed to reveal any other case of creeping eruption due to a hookworm larvae acquired in Massachusetts.

Factors probably responsible for the rarity of creeping eruption in New England are considered.

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MEDICAL PROGRESS

SURGERY OF THE AUTONOMIC NERVOUS SYSTEM

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THE following phases of the surgery of the autonomic nervous system will be considered: operations on the sympathetic division; the pathologic and physiologic aspects of the hypertensive state; and operations on the parasympathetic division.

OPERATIONS ON THE SYMPATHETIC DIVISION

The treatment of hypertension and hypertensive cardiovascular disease by operations on the sympathetic division of the autonomic nervous system continues to be the topic of greatest current interest in this field of surgery. The rationale was well stated by Rowntree and Adson[1] in 1925 in what appears to be one of the first articles on this subject. The authors discussed their experiences with 2 patients treated, respectively, by periarterial sympathectomy of the left femoral artery and lumbar sympathectomy. Since the treatment of a great many patients with malignant hypertension had ultimately been disappointing, it occurred to Rowntree and Adson that relative freedom from vascular spasm might be attained through the removal of the vasoconstrictor influence of the sympathetic nerves on the vessels of the leg. It was thought that this might not only lower the systemic blood pressure but also provide simultaneously an area of diminished resistance that would give way under strain and thereby serve somewhat in the capacity of a safety valve for the protection of the cerebral and retinal vessels. In other words, it was their concept that sympathectomy might decrease the peripheral resistance to blood flow and thus result in a lowering of the blood-pressure levels. Also, fluctuations of blood pressure might be minimized, the intermittent stress and strain on the vascular bed being thereby reduced. Although over twenty years have passed since this original attempt to modify the course of hypertensive cardiovascular disease by therapy of this sort and although various suggestions have been made to account for favorable results, no likelier explanation has been advanced to date. Proof of the nature of the effect must await detailed physiologic studies before and after operation. These, unfortunately, have not as yet been carried out in sufficient detail to be conclusive. Discussion so far has therefore centered about objective evidence, such as changes in blood pressure or the reversal of cardiovascular damage that existed prior to operation.

Extent of Operation

Because periarterial sympathectomy and lumbar sympathectomy had little effect on blood pressure, Adson,[2] in 1930, extended the operation to include the splanchnic bed. A laminectomy was performed, and the anterior roots were sectioned bilaterally from the sixth thoracic to the second lumbar segment, inclusive. This operation was much more effective but had to be abandoned because of the high mortality and morbidity. Alternate procedures were developed in fairly rapid succession, including the subdiaphragmatic technic of Craig[3] in 1934, the supradiaphragmatic splanchnicectomy of Peet[4] in 1935 and the lumbodorsal or thoracolumbar splanchnicectomy of Smithwick[5] in 1940. These operations have a similar purpose — namely, to denervate a large vascular area (the splanchnic bed) that contains a large portion of the arterioles of the body. It is generally believed that in hypertensive patients, the increased peripheral resistance to blood flow is offered by vessels of this size. The operative mortality has been low. In 1941 Grimson[6] suggested that total thoracic or total sympathectomy might be more effective. The purpose of these more extensive procedures was to include the heart in the denervated area. Grimson was led to believe that this was indicated as a result of his experiences with dogs in which experimental neurogenic hypertension could not be significantly modified unless the heart was included in the denervated area. As might have been expected, the mortality of these more extensive procedures was considerably higher than that of the various forms of splanchnic denervation mentioned above. The percentage of successes in unselected cases seemed not appreciably higher than that for the lumbodorsal technic, although it should be stated that Grimson's series was not large enough to be fairly evaluated at that time. Further reports will be awaited with interest. In a recent review Grimson[7] expressed the opinion that clinical experience with the treatment of hypertension indicated that elimination of abnormal reflex vasoconstrictor tone of central origin more effectively reduces blood pressure as sympathectomy of the body is made more and more complete.

In the recent literature a number of articles have appeared describing modifications of the lumbodorsal technic. Klemme and Woolsey[8] separated the diaphragm from the bodies of the twelfth dorsal

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and upper two lumbar vertebras without dividing the muscle. Otherwise, the extent of the operation remained unchanged — that is, removal of sympathetic trunks from the eighth thoracic to the first or second lumbar ganglion, inclusive, and of the great splanchnic nerves from the celiac ganglions to the midthoracic level. Poppen[9] removed a segment of the tenth or eleventh rib, instead of the eleventh and twelfth, and obtained a lumbar exposure below the twelfth rib, working above and below the diaphragm without dividing the latter. The extent of the removal of the sympathetic trunks and splanchnic nerves is from the seventh or eighth thoracic segment to the second or third lumbar ganglion. More recently, Hinton and Lord[10] suggested a variation in which a segment of the ninth or tenth rib is removed, the diaphragm is divided transversely from above and the sympathetic trunks, together with the splanchnic nerves, are removed as a rule from the third or fourth thoracic segment to the second lumbar ganglion inclusive. The operation is carried out either extrapleurally or transpleurally. They correctly point out that this operation is of greater magnitude and more serious for the patient, and that it is entirely conjectural whether the late results will show any greater benefit. If my concept of the origin of the vasoconstrictor nerves to the splanchnic bed is correct, it does not seem likely that these more extensive procedures will result in a more thorough denervation of this area. From my point of view, the most logical reason for extending this operation is to include the cardiac innervation, which the variations mentioned above do not accomplish. In a number of failures following lumbodorsal splanchnicectomy I have extended the operation subsequently to total sympathectomy to include the heart, so far without notable success. It is possible, however, that in certain cases cardiac denervation should be a part of the original maneuver. It is believed that lumbodorsal splanchnicectomy as described[5, 11, 12] is the procedure of choice in the great majority of selected cases of continued hypertension because it offers a 75 to 85 per cent chance for improvement at an operative risk of less than 1 per cent.[13]

Results of Surgical Treatment

Peet[14] has recently discussed the late results in a series of 437 cases operated on by his supradiaphragmatic technic. The patients had been followed for five to eleven years. In 82 per cent serious organic disease was demonstrable prior to operation. Two hundred and fifty-one, or 57.5 per cent, were alive at the time of follow-up study.

Of patients with symptoms and fundus changes but without cerebral, cardiac or renal involvement, 95 per cent were living five to eleven years after operation. These represented 17 per cent of the total series. Of these, 30 per cent had normal blood pressures, and another 47 per cent had maintained significant reductions. Symptoms had been completely relieved or definitely improved. Angiospastic retinal changes had been improved in a remarkably high percentage of cases. Normal electrocardiograms, heart size and kidney function had been adequately protected. Approximately a third of all the patients who showed preoperative evidence of organic heart disease, cerebrovascular disease or impaired kidney function did not survive five to eleven years. Half the patients who fell into these categories maintained significant blood-pressure reductions for the same period of observation. Symptomatic improvement occurred in a high percentage, apparently being present in as many of this group as in the most favorable cases mentioned above. Sixty per cent of patients who had suffered a cerebral accident had no recurrence of this complication after splanchnicectomy.

Of the cases with malignant hypertension, 19 per cent were alive five to eleven years after operation. These patients had severe neuroretinitis with papilledema of 1 diopter or more prior to operation. The usual mortality for such cases prior to the advent of surgery was approximately 80 per cent within one year, 90 per cent within two years and 99 per cent within five years.[15]

Experiences with lumbodorsal splanchnicectomy in the treatment of hypertension and hypertensive cardiovascular disease have been discussed by Ayman and Goldshine,[16] de Takats, Heyer and Keeton,[17, 18] Hinton and Lord,[19] Ray[20] and Smithwick[11–13, 21, 22] and in numerous communications by White et al.[28–30] These authors appear to be in agreement that surgery is a useful adjunct in the management of the hypertensive patient. White et al. have emphasized the favorable changes observed in the hypertensive heart, particularly improvement as demonstrated in the electrocardiograms and heart size and function. Favorable changes also occur in eyegrounds and in renal function as judged by ordinary tests, as well as symptomatic improvement. The early indications are that life expectancy will be materially improved.

Selection of Patients for Surgery

In a recent review of the results of lumbodorsal splanchnicectomy in a series of 439 cases followed for one to eight years, the selection of patients for surgical treatment is discussed in considerable detail.[13] A standard method of study is described that was designed to obtain similar data in all cases and thus to subdivide patients into more comparable categories. All the cases in this series had reached the stage of continued hypertension, and 97 per cent had demonstrable cardiovascular damage prior to operation. These were an unselected group of patients. Over 60 per cent were improved when judged by both blood-pressure data and favorable changes in cardiovascular damage. These results

were carefully studied, and certain rules were discussed by means of which the patients who had done poorly and those who had the smallest statistical chance for a worth-while result could be excluded with reasonable certainty. The suggested rules apply to about 30 per cent of patients with continued hypertension and cardiovascular changes, leaving 70 per cent that could be regarded as selected cases. In these, there was a 75 to 85 per cent chance for a favorable effect on both the blood pressure and the cardiovascular system following operation. In addition, 11.3 per cent showed no progression. The total mortality from all causes, including operative mortality and deaths unrelated to the disorder in question, for the follow-up period of one to eight years was remarkably low, 98.8 per cent of the patients being alive at the time the analysis was made. This series comprised many cases with previous cerebrovascular accidents, abnormal electrocardiograms and enlarged hearts and some with congestive failure or previous coronary thromboses, as well as definite evidence of renal disease as judged both by tests of function and by the study of biopsy material obtained at operation. It is expected that a larger experience and a longer follow-up period will suggest further rules designed to improve accuracy in the selection of cases for this form of treatment. Because of the amount of data that have been obtained in the study of each case, it is expected that when the series is larger it will be possible to divide the cases into many smaller groups, so that almost any hypertensive patient will fall into one of them. The effect of surgery of this sort on blood pressure, the cardiovascular system and life expectancy can then be foretold accurately. Such variables as sex, age and the severity of the hypertension — as judged by the resting horizontal diastolic level, the width of the pulse pressure and the state of the brain, eyegrounds, heart and kidneys, as well as the response to sedation and other transient methods of inactivating sympathetic activity — will have to be held constant in each subgroup. One of the great difficulties about any discussion of the results of surgical treatment of hypertensive patients at present is the fact that no such comparable data for nonsurgically treated patients are available for comparison. Consequently, these results are open to as much criticism as anyone wishes to level at them. In any event nobody questions the facts that the complications of hypertension are responsible for more deaths annually than any other human disorder and that a reduction of this mortality rate and an increase in the life expectancy of this group of patients are highly desirable. To meet the objection mentioned above the natural course of a control series of similarly studied patients who have not as yet been subjected to surgery is being followed. It is essential that the method of study be comparable in every respect. It would not be proper, for example, to compare patients with transient or intermittent hypertension with those who have passed through this phase and have reached the stage of continued hypertension in which the diastolic pressure no longer falls to normal after a period of bed rest. Nor would it be proper to compare cases of continued hypertension without cardiovascular changes with those having damaged vascular beds. The latter is the group with which I have been primarily concerned to date. If a simple panacea for this disorder is ever discovered, it will undoubtedly be found to be most effective if employed before the vascular bed is damaged. The same thing will probably be true of surgical treatment. Earlier operation has been suggested by White,[29] Landis[31] and de Takats.[18]

In the recent literature the use of spinal anesthesia by one technic or another has been advocated as a means of selecting cases for surgical treatment.[32, 33] The data so far presented do not appear to be significant. Also, the effect of newer sympatholytic drugs has been described.[34, 35] It seems unlikely that any diagnostic procedure that has a transient effect will be the entire answer to this difficult problem. There may be an adequate correlation in patients who respond well to those temporary measures and the effect of operation. There will probably be an unsatisfactory correlation in those who do not respond well to tests but who do benefit by surgery. The matter appears to me to be a little too complex to be amenable to solution in this fashion. It also seems likely that at least a part of the favorable effect of sympathectomy cannot be measured by changes in blood-pressure levels alone.

Pathological and Physiologic Aspects of the Hypertensive State

Although the primary purpose of the surgical treatment of these patients has been to lessen the severity of the hypertension, to reverse cardiovascular changes when possible and to increase life expectancy, it has been realized that this approach to the problem has offered a unique opportunity to obtain factual data concerning the pathologic physiology of the hypertensive state. In particular, it has been possible to visualize the kidneys at operation and to obtain specimens for microscopical study. Ever since Richard Bright[36, 37] first called attention to the entity of hypertension and the role of the kidney in the production of increased tension within the vascular bed, opinions have varied concerning the importance of the renal vascular area in the genesis of this disorder. The demonstration by Goldblatt[38] that reduction of blood flow through this area by clamping of the renal arteries resulted in chronic hypertension in animals has further stimulated interest in this matter. The detailed studies of Moritz and Oldt,[39] notwithstanding the discussion of this matter in 1872 by Gull and Sutton,[40] added further impetus

to this school of thought. Physiologic studies, particularly renal-clearance observations by Smith,[41] abundantly corroborated by others,[42] have, together with biopsy material,[43, 44] cast considerable doubt on the primacy of renal arteriolar disease as the usual causative mechanism. The evidence has been reviewed in some detail, the essential conclusions being that data pertaining to the gross appearance of the kidneys, accumulated during the course of the surgical treatment of hypertensive patients, indicate clearly that contracted granular kidneys do not antedate the hypertensive state in man. The following conclusions are drawn[45, 46]:

> For the first time, an opportunity for the microscopic study of renal arterioles of living patients with continued hypertension has presented itself. The findings are also at variance with autopsy material. They suggest that pre-existing renal arteriolar disease of a moderate or marked degree is not a sine qua non to the hypertensive state.
>
> For the first time, an opportunity has arisen whereby the pathological changes can be correlated with the physiological state of the kidney. It has been noted that neither a marked reduction in quantity (ischemia) nor a change in the nature of renal blood flow (constriction of the efferent glomerular arterioles) is obligatory to the hypertensive state.
>
> When renal vascular disease and hypertension are associated, it is difficult to disprove a cause and effect relation; and no one questions the importance of renal disease, when present, as a factor in human hypertension. However, to make this the universal explanation for hypertension in man is not in keeping with the facts. A concept is needed, which will explain the cause of hypertension in the absence of kidney disease, and the absence of hypertension in the presence of kidney disease.
>
> The surgical treatment of hypertension has introduced a new factor, the autonomic nervous system, into the already complicated picture of the hypertensive state in man. It has contributed data which cast doubt upon the primacy of renal arteriolar disease as the sole causative factor.

It is most desirable that the explanation for reduction of blood pressure following splanchnicectomy be determined, since this may lead to a clearer understanding of causative mechanism. It might also lead to the development of accurate methods of selecting cases for this form of treatment. It might indicate productive lines for future investigative work. More detailed studies of the cardiovascular system in hypertensive patients are obviously indicated and may yield information of great value that cannot necessarily be obtained in the experimental laboratory. Collaborative efforts of physiologists, pharmacologists, biochemists and clinicians are needed to accomplish this purpose. Already, a beginning has been made in this direction, and important evidence is being accumulated as a result of such studies. Talbott et al.[44] measured the blood flow through the renal area before and after lumbodorsal splanchnicectomy in a series of 20 cases. Prior to operation a wide variation was noted — from normal levels to a marked reduction. The authors were unable to detect any significant alteration in renal blood flow after operation regardless of the effect on the blood pressure. Further studies of this sort are indicated. More recently, Stewart et al.[47] studied the part of the volume output of blood from the heart that is allotted to the peripheral circulation. These observations were made in normal subjects and in patients with hypertension. A trend toward a decrease in peripheral blood flow was found when there was hypertension, with a rise in the rectal and a decrease in the average weighted skin temperature. The temperature of the upper part of the body was warmer and that of the lower part cooler in hypertensive subjects than in those in the same age groups with normal blood pressures. The reduction in peripheral blood flow to the lower part of the body is greater than the increase in the upper part of the body so that the net result is an average peripheral blood flow for the whole body in hypertensive subjects that is less than the value in normal young men at the same room temperature.

Stewart et al.[48] studied the peripheral blood flow in a series of hypertensive patients before and after splanchnicectomy by various technics. They found lumbodorsal splanchnicectomy to have the greatest effect on the blood pressure. Following this operation, the blood flow in the upper portion of the body, which tended to be increased in hypertensive patients prior to operation, consistently fell somewhat. In the trunk and lower portion of the body, where the tendency in untreated hypertensive patients was toward a decrease, the blood flow remained the same or increased. An increase in blood flow was consistently noted in the distal portion of the lower extremity. The over-all amount of blood allotted to the periphery in hypertensive patients in whom the blood pressure fell to normal after operation increased in some patients and decreased in others. The change was not statistically significant. In another group of patients in whom there was no lowering of blood pressure following operation, the change in peripheral blood flow was not significantly different from that in the group mentioned above. These findings are similar to those of Talbott et al.[44] and others[49, 50] regarding blood flow through the renal area before and after splanchnicectomy, there being no obvious relation between blood flow and blood pressure. Stewart et al.[48] reached a similar conclusion concerning peripheral blood flow: "The level of blood pressure has no relation to peripheral blood flow either where the blood pressure is high or in the same patient after restoration of normal blood pressure." This viewpoint is of interest and of importance since it is not in keeping with the concept that hypertension is essential to the maintenance of adequate circulation to the tissues that is held by those who believe that elevated blood pressure results from vascular disease and is a compensatory mechanism. It is in keeping with clinical experience indicating that lowering of blood pressure by splanchnicectomy is helpful, not harmful, in the majority of hypertensive patients and is attended by improvement in the state of the cardiovascular system as judged by

favorable changes in the cerebral, retinal, cardiac and renal areas, as well as in symptoms. Stewart et al. also noted that the rectal temperature, which was elevated in hypertensive patients, fell after operation. Also, in patients who experienced a fall in blood pressure to normal there was a decrease in the mean basal metabolic rate. In patients in whom there was no change in blood pressure there was no change in the basal metabolic rate. Studies of this sort are significant, representing the beginning of what must be determined to explain the mechanism whereby blood pressure is lowered following surgery. The crucial questions are whether sympathectomy lowers blood pressure by affecting active causative mechanisms of a physiologic nature, or whether the effect is due to a change in hemodynamics that counteracts hypertension. Why does splanchnicectomy fail to affect hypertension in certain cases? The correct answer to these questions may have an important bearing on the cause of hypertension in man.

Operations on the Parasympathetic Division

With the exception of sporadic attempts to relieve bronchial asthma by resection of vagal fibers to the lung, little has been attempted in the way of surgery of the parasympathetic nervous system. In recent years reports of experiences with resection of the vagus nerves to the stomach in the treatment of peptic ulcer have appeared in the literature. The early results seem encouraging and suggest that vagectomy may prove to be a useful adjunct to other measures available for the management of this disorder. A widespread interest has developed, and it is to be expected that the possibilities of this therapeutic measure will be explored in many clinics and that the literature on this subject will increase considerably in the next few years. As with everything that is new, the test of time will have to be applied before a final evaluation of results can be made.

Perhaps it is not quite correct to refer to vagectomy as a new procedure. Physiologists have been familiar with it for many years and have studied its effect on gastric function in great detail. One of the earliest references to its application in man is a report by Pieri[51] in 1932. He performed bilateral subdiaphragmatic resection of the vagus nerves in 14 patients for the relief of gastric disorders, and stated that the operation was well tolerated and did not cause appreciable untoward incidents. The report that stimulated current interest in this matter was that of Dragstedt and Owens[52] in 1943. Their first 2 patients were operated on in January and February of that year. Since that time additional reports of progress have been made by Dragstedt and his associates.[53, 54] Moore et al.[55] and Grimson[56] have also reported early results.

Rationale of Vagectomy for Peptic Ulcer

In their writings to date, Dragstedt et al. have stressed the use of vagectomy in cases of refractory and complicated ulcer. Most of their subjects have been men with long-standing duodenal ulcers with or without previous surgery. They have also stressed the effect of this operation on the first period of gastric secretion — namely, that of interdigestive or continuous secretion. To obtain data on this matter, they collected gastric juice for twelve-hour periods from 9:00 p.m. to 9:00 a.m. by continuous suction, the stomach having been emptied and washed out prior to the collection period. The average findings for at least three such periods of observation prior to operation in 10 patients with refractory ulcer who had had no previous surgery were as follows: volume, 821 cc.; free acid, 47 units; and total acid, 66 units. Following operation, the corresponding values were 335 cc., 15 units and 46 units. In 9 cases of complicated ulcer the findings before and after vagectomy were similar. Some of these patients were obstructed, and a gastroenterostomy was also performed; others had had previous gastric resections or gastroenterostomies. In the discussion of the paper in which these results were reported, Grimson indicated that the twelve-hour night-secretion volumes in his series of 18 cases were reduced from an average of 946 cc. before operation to one of 342 cc. after operation. The acidity expressed in terms of pH was changed from an average of 1.72 before to 3.55 after vagectomy. These findings are of interest, not only because they indicate at least one clear-cut physiologic effect of the operation but also because they cast additional light on the explanation for the period of continuous gastric secretion. As recently as 1941 Ivy,[57] in an excellent discussion of the mechanisms of gastric secretion, indicated that the nature of the stimuli that give rise to the continuous secretion of gastric juice is uncertain. He stated that some patients, particularly those with a duodenal ulcer, manifested a hypernormal continuous secretion — that is, the stomachs continued to secrete a copious quantity of acid juice after emptying. He suggested that this might be due to the production of histamine by an irritated mucosa, since atropine in relatively large doses does not abolish abnormal continuous secretion whereas it has a significant effect on normal gastric secretion as shown by Keefer and Bloomfield.[58]

In addition to the effect of vagectomy on the first period of gastric secretion, it seems probable that certain aspects of the second are favorably affected. This period may be divided into three phases: the cephalic, the gastric and the intestinal. The first is known to be under the control of the vagus nerves. Stimuli such as sight, smell, taste and thought of food result in gastric secretory activity mediated by the parasympathetic nervous system. Certain

other stimuli, particularly some of an emotional variety, may cause increased vagal activity and acid secretion. There is no reason to doubt that the secretory response to these stimuli is inhibited by vagectomy. Thus, an over-all effect of this operation is to reduce both continuous and intermittent gastric secretion of neurogenic origin. Its efficacy in the treatment of some duodenal ulcers may depend on the extent to which the first period of gastric secretion, the cephalic phase of the second period, and other neurogenic or psychosomatic mechanisms enter into the problem at hand. It is true, however, that in other ulcer patients there is little evidence of an abnormality of neurogenic secretory mechanisms. Whether there will be any great effect on either the gastric or the intestinal phase of the secretory process awaits further study. These are thought to be largely under the control of chemical substances of a histamine-like nature. After vagectomy, a response to histamine or caffeine still persists, although in some cases a reduction has been noted following histamine, as pointed out by Grimson.[56] The explanation for the latter is not clear.

In addition to these reported changes in gastric secretion, an alteration of gastric and intestinal motility is noted, particularly in the immediate postoperative period. This is evidenced by a delay in the initial as well as the total emptying time of the stomach. Its tone and reactivity are likewise decreased. These changes become less marked in the course of months and are rarely attended by symptoms of consequence. Whether these motility changes have any beneficial effect on the healing of peptic ulceration is not known.

Grimson[56] believes that although changes in secretion and acidity are important, the most pronounced and consistent change produced by vagectomy is the decrease in motility of the stomach. On the other hand, Dragstedt[59] points out that in experimental animals in which gastric juice is allowed to be in contact with the intestinal mucosa when the alkaline duodenal secretion has been shunted distally (as in Mann–Williamson dogs) ulcers regularly develop. In these animals the motility factor has probably not been materially altered. In almost all reported cases the relief of symptoms, particularly pain, has been dramatic, immediate and persistent. Nearly all ulcers have healed promptly. The effect of operation has so far been particularly gratifying in the group of troublesome cases in which gastrojejunal ulcerations have developed following gastric resections. The relief from pain is of interest since it is not associated with evidence that pain pathways have been divided as judged by postoperative balloon-distention observations. Pain is still perceived in response to stimulation of the esophagus, duodenum and jejunum[55] and when hydrochloric acid is introduced into the stomach.[59] It therefore appears that relief is more probably due to decreased acidity or motility or to both.

Surgical Technic

An excellent review of experimental work in this field and of the earlier attempts to perform an effective interruption of the vagal innervation of the stomach in man was recently published by Weinstein et al.[60] Partial division of the vagal fibers to the stomach by vagotomy for the relief of peptic ulcer was performed by Stierlin in 1920, Bircher in 1921 and Schiassi in 1925. In 1937 Barron and Curtis divided the left (anterior) vagus nerve in a case of gastric hypertonia. Winkelstein and Berg[61] combined anterior vagotomy with subtotal gastrectomy for duodenal ulcer in patients with high gastric acidity in 1938. In all these operations, an abdominal approach was used. The denervation was only partial.

To study the relative merits of partial and total parasympathetic denervation of the stomach Weinstein et al.[60] studied the behavior of three types of gastric pouch in dogs: the Heidenhain pouch, which receives no vagus innervation; the Pavlov pouch, in which only a small percentage of vagal fibers remains intact; and the so-called "vagal" pouch, in which practically all the vagal fibers are unsevered. The secretory responses to the ingestion of food, as measured by the acidity curve, were found to be essentially the same in all varieties of pouches. When, however, a stimulus was applied that operated through the nervous system, good secretory responses were noted in the totally and partially innervated pouches, being equally marked in each. This is an important observation, since it confirms a general law that has been previously learned in surgery of the sympathetic nervous system — namely, that a denervation must be complete to be effective. In only the Heidenhain pouches (totally denervated) was there no secretory response to this stimulus. Weinstein et al. believe the insulin test to be an effective indicator of the completeness of denervation following vagectomy in man. It is performed on a fasting stomach with a tube in place. The contents are aspirated, and 15 units of regular insulin is injected intravenously. Following this, gastric specimens are withdrawn every fifteen minutes for three hours, and blood sugar determinations are made at the beginning of the test and every half hour for one and a half hours. In 6 cases in which various types of vagectomies and vagotomies were performed, evidence of incomplete denervation was found after operation as judged by a significant acid secretory response to insulin. This led the authors to conclude that complete parasympathetic denervation of the stomach was impractical in man. Dragstedt et al.[54] and Moore and his associates[55] found the postoperative response to insulin to be abolished. Grimson[56] reported a variable reduction. My own experiences indicate that vagectomy has so far been uniformly successful in abolishing or greatly reducing postoperative

insulin secretion as well as greatly modifying the volume and acidity during the continuous period of gastric secretion. Also, vagectomy has had a greater effect than preoperative atropine block on this period of gastric secretion. In some cases the response to histamine has been definitely reduced.

Successful bilateral vagectomy may be performed by either a transthoracic or an abdominal approach. In the former, an extensive resection of the seventh or eighth rib on the left side is advocated by Dragstedt and Schafer.[55] I have found this to give an excellent exposure of the operative field. The vagus nerves are quite readily exposed above the diaphragm and divided at this level. The various branches that form a network about the esophagus are gathered into two bundles and freed for about 10 cm. above the diaphragm. The upper ends are sutured widely apart by Dragstedt, and the pleura closed. It has been my custom to encase the nerves in a silk cylinder as a further precaution against regeneration — a maneuver that has been used elsewhere[62] in surgery of the autonomic nervous system. Moore et al.[55] have reported the use of this step in technic and in addition have divided the diaphragm and followed the branches of the vagi to their terminations in the stomach wall for additional protection against regeneration. So far, no definite evidence of this has been reported in the literature following supradiaphragmatic resection. A recent conversation with Dragstedt reveals that the patients in his earliest cases, who were operated on nearly four years ago, continue to do well.

The abdominal approach is useful when some additional procedure is indicated or when exploration of the lesion is considered advisable. In certain cases, particularly those with a high degree of obstruction combined with hypersecretion of the continuous variety, vagectomy has been combined with gastroenterostomy or gastric resection. If the left lobe of the liver is mobilized by division of its peritoneal attachment to the diaphragm, the esophagus is readily exposed. After its anterior peritoneal covering has been incised, dissection can be carried upward quite readily for about 6 cm. above the diaphragm, and this portion of both the anterior and the posterior vagus nerves and their branches resected. In proper hands and under ideal circumstances it is apparent that these operations can be performed with an extremely low mortality and with few complications.

The Selection of Cases for Surgery

The writings of Dragstedt et al. have emphasized the significance of the first period of gastric secretion. They have indicated that hypersecretion has been present in the great majority of their patients. Their data suggest that the patients who exhibit this abnormality may be the ones who are likeliest to do poorly after subtotal gastrectomy. So far as the cephalic phase of gastric secretion is concerned, it appears that studies of sham feeding have not revealed any conclusive evidence of abnormal responses in ulcer patients. Such reactions as exist should be modified by vagectomy. Moore et al. emphasize the importance of the history in ulcer patients, particularly evidence pertaining to the effect of stress and strain on symptoms. They regard young and middle-aged patients, who are most frequently men, with chronic ulcers that recur under stress and strain and are only transiently relieved by food or alkali as ideal subjects for operation. Previous perforation or hemorrhage is not considered a contraindication. Vagectomy should not be performed in their presence. The question of obstruction and its management by additional procedures such as gastroenterostomy and gastric resection remains for future evaluation. Because of increasing evidence pointing toward the danger of carcinoma in the presence of gastric ulceration, it appears inadvisable in general to treat cases of this sort by vagectomy. The early results of vagectomy are encouraging and warrant further study of its use in patients with duodenal ulcers requiring surgical treatment. It will be some time before the relative merits of and the indications for gastric resection and vagectomy are established.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33181

PRESENTATION OF CASE

An eighty-nine-year-old widow entered the hospital from a convalescent home because of oliguria.

The patient was unable to give a reliable history, and the only information that bore up under repeated questioning was that three weeks before hospital entry she had developed a cough productive of thick, yellow sputum and fever, nausea and abdominal soreness, with anorexia so severe that she took little food or water. Her physician disclosed that she had been given 120 cc. of Aldiazol, a liquid sulfadiazine preparation, over a two-day period. Four days before entry the urinary output dropped markedly, so that only 180 cc. of urine had been passed in the forty-eight hours before admission. The patient had previously noted darkening and reddening of the urine, but the volume seemed to have remained fairly normal. She denied backache and dysuria. Although she had eaten little during this time, she had drunk considerable fluid.

The past history revealed that she had had shortness of breath on exertion but no anginal pain. For several years she had taken digitalis irregularly. She had long been constipated and had used laxatives regularly for more than a year. She had never had any children, the ovaries having been removed many years previously for an unknown reason.

Physical examination revealed a moderately obese woman with a dry tongue. Although the memory was poor, she was alert and co-operative. The chest was emphysematous, with a moderate number of fine moist rales at both bases posteriorly. The area of cardiac dullness was obscured by emphysema. No murmurs were heard. There was slight tenderness in the right upper quadrant. The liver and spleen were not palpable. There was tenderness in both costovertebral angles, especially on the right. Pelvic examination revealed some tenderness on motion of the cervix upward. No masses were felt.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 65 diastolic.

Three cubic centimeters of dark-brown urine was obtained by catheter, and analysis showed a pH of 7.5, a + test for albumin and no sugar; the sediment contained numerous fresh red cells, many epithelial cells and 1 or 2 white cells per high-power field. No bacteria or casts were noted. Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 10.5 gm., and a white-cell count of 24,000, with 91 per cent neutrophils. The nonprotein nitrogen was 133 mg. per 100 cc. The sodium was 137.3, the potassium 6.3, the carbon dioxide 31.0 and the chloride 95 milliequiv. per liter. The blood was examined for sulfadiazine, but no trace was found.

X-ray examination of the chest showed cardiac enlargement, the cardiothoracic ratio being 13:23, but the configuration was not characteristic of any particular lesion. The wall of the aorta showed calcification. No fluid was present in the pleural sinus, and there were irregular areas of increased density at both bases. The pulmonary markings were everywhere a little prominent, but no gross areas of collapse or consolidation were seen. A plain film of the abdomen showed gas-filled loops of large bowel and of a portion of the small bowel, possibly ileum. Cystoscopy and retrograde pyelograms were negative. No urine, however, was obtained from either pelvis. Instilled fluid returned clear from the right pelvis and slightly blood tinged from the left.

During the next few days there was no improvement. The patient passed no urine, 30 cc. of bloody urine being obtained by catheter on the third hospital day. The fluid intake averaged 600 cc. a day. The costovertebral-angle tenderness persisted, and nausea, muscular twitching and a positive Chvostek sign developed. The nonprotein nitrogen rose to 154 mg. per 100 cc. On the fourth hospital day the patient expired.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES L. SHORT: The first question that we must answer is, What was the nature of the original infection that apparently began three weeks before admission? This was presumably in the respiratory tract and suggests bacterial pneumonia. Perhaps we shall be helped by the x-ray films of the chest. May we see them now?

DR. STANLEY WYMAN: I do not believe that the films will be helpful. They show a large heart and a few small, indefinite linear areas of density in both bases, which, I suppose, lie in the lower lobes. I do not see frank consolidation.

DR. SHORT: Does that picture suggest infection rather than congestion?

DR. WYMAN: It is the picture one sees in atelectasis in any patient lying in bed with some impairment of diaphragmatic motion.

DR. SHORT: Does the film of the abdomen show any definite point of obstruction or rather suggest ileus?

DR. WYMAN: The film of the abdomen is more in keeping with ileus than with true intestinal obstruction.

The retrograde pyelogram shows good calyxes, pelves and ureters on both sides.

DR. SHORT: There is no definite evidence of pneumonia at the time of admission. We also have nothing to suggest any marked degree of pulmonary edema. The patient had no fever when she entered the hospital, which suggests that the infection, whatever it was, had cleared. The high white-cell count can probably be explained by a renal injury.

The next question and the chief one to answer is, What was the cause of the anuria and uremia that were evidently responsible for this woman's death? I am unable to decide from the evidence at hand that any of the usual forms of nephritis were present, although an acute glomerulonephritis secondary to infection could produce a clinical picture somewhat similar to this. The lack of fever is against a suppurative lesion of the kidney, and such rare conditions as dissecting aneurysm involving the renal arteries and renal infarction, I believe, we need mention only in passing.

I am forced to conclude that the renal shutdown was directly connected with the sulfonamide preparation taken by the patient. This preparation, I have been informed, contains 1.5 gm. of sulfadiazine and an equal amount of sulfathiazole per 30 cc., with additional sodium citrate and sodium lactate in an aqueous solution, so that we do not need to worry about a toxic solvent's being involved. In the dosage given this patient received 6 gm. of each drug, which does not seem excessive over two days, and we know that the solubility of the drugs was probably enhanced by the mixture of equal parts of each drug and by the additional alkali. For this reason, as well as the lack of severe pain, the absence of crystals in the urine and the negative findings on washing of the kidney pelves, I have decided against obstruction of the kidney pelves or the ureters by sulfonamide concretions as the cause of the anuria. These considerations do not rule out obstruction in the tubules themselves by sulfonamide crystals, but I prefer to believe that the anuria was due chiefly to a direct toxic action on the renal parenchyma. Such a process has been clearly described pathologically without evidence of obstruction by crystals, although it is less frequent as a cause of sulfonamide renal impairment than obstruction.

I might mention still another possibility: that the renal damage was due to an acute hemolytic anemia resulting from sulfonamide administration. These cases occur nearly always with sulfanilamide, and we should expect jaundice and a severer degree of anemia to be present. As a matter of fact, if such an anemia had occurred, the pathological findings would have been closely similar to those that I expect to be found in this patient.

Before concluding, I should like to attempt to answer a few more questions. It would be interesting to know whether or not previous administration of sulfonamides had taken place, so that the severity and the abruptness of the reaction could be explained on the basis of hypersensitivity. We are not helped by the history, and there were no other manifestations of sensitivity, such as fever and dermatitis. It is still possible that focal lesions in the heart and other organs will be found or even vascular changes resembling periarteritis nodosa, as described by Rich.[1,2] But the short duration of administration of the drugs makes this unlikely unless the patient had previously been sensitized. Whether or not she had pre-existing renal disease that had made her especially susceptible to sulfonamide intoxication, I do not believe that we can find out, although the negative pyelogram helps rule out certain anomalies and diseases of the kidney. The site of damage in the group to which I think this patient belonged is usually the distal portion of the tubules, with involvement also of the interstitial tissue — so-called "lower-nephron nephrosis." A similar clinical picture can be produced by cortical necrosis. I have seen a reference to this condition that was presumably caused by sulfonamide intoxication,[3] but I do not believe that we need consider it in the case under discussion.

In summary, I believe that the primary cause of death in this patient was uremia resulting from tubular necrosis caused by sulfonamides, with cardiac enlargement and arteriosclerosis as additional diagnoses. I do not believe that I can say anything about the changes in the lungs, unless edema developed before death. In a woman of this age other abnormalities or landmarks may well have been present, but I shall not try to predict what they were.

DR. TRACY B. MALLORY: Dr. Dahl, will you tell us what the impression was on the ward?

DR. LOUIS K. DAHL: In general the house staff believed that the diagnosis rested between three main possibilities: acute glomerulonephritis, with golden shutdown; interstitial nephritis due to sulfonamides; and — one person thought — bilateral cortical necrosis. The most prevalent opinion was interstitial nephritis caused by sulfonamides.

CLINICAL DIAGNOSIS

Interstitial nephritis, caused by sulfonamides.

DR. SHORT'S DIAGNOSES

Lower-nephron nephrosis, due to sulfonamide toxicity.
Cardiac enlargement.
Arteriosclerosis.

ANATOMICAL DIAGNOSES

Periarteritis nodosa.
Diffuse cortical necrosis, secondary.
Arteriosclerosis.
Hypertrophy of heart.
Pulmonary emphysema.
Cholelithiasis.

Pathological Discussion

Dr. Mallory: Autopsy showed interesting kidneys. They weighed 450 gm., and for a woman of eighty-nine that is significant hypertrophy. The surfaces were mottled and purplish red, and the capsules stripped fairly readily. When the organs were cut it was found that the entire cortex of both kidneys was infarcted, presenting the gross picture of diffuse cortical necrosis. This is seen most frequently — in about 2 out of every 3 cases, I should say — in young women during the terminal stages of pregnancy or in the first few days following delivery. At the age of eighty-nine that possibility need not be considered. Cortical necrosis has been seen in a scattered variety of other conditions and is occasionally seen in male patients.

When we examined the sections of the kidneys microscopically another possibility was brought up. In all sections there were many small arteries showing the typical changes of periarteritis nodosa. A few arteries outside the renal substance also showed the same lesion — few indeed, but some. There was a characteristic lesion in one adrenal gland, a few changes in the perirenal fat tissue, and a single lesion in the heart. Diffuse involvement of the small renal arteries with periarteritis nodosa might produce the same total infarction of the cortex that one sees in so-called "primary cortical necrosis." I think that the way in which this case should be classified remains debatable. The facts that the arterial lesions were so characteristic of what one sees in periarteritis nodosa and that at least a few lesions were found in organs other than the kidneys lead me to make periarteritis nodosa my primary diagnosis.

The other changes found were only those that one might expect to find in a very old person, — extremely severe arteriosclerosis of the aorta, with multiple ulcerated atheromas and secondary thrombi, — but the main renal arteries were not markedly involved. The heart was hypertrophied, and the lungs were emphysematous; the gall bladder was filled with small stones, and the bile ducts were patent.

Dr. Short: What did the tubules show?

Dr. Mallory: The glomeruli and all tubules in the cortex were completely necrotic, a picture exactly like that of infarction, except that it was symmetrical and diffuse throughout the entire cortex of both organs.

Dr. Fletcher H. Colby: Were you able to determine which arteries were responsible?

Dr. Mallory: In cases of idiopathic cortical necrosis, vascular changes are variable and inconstant. There are usually necrosis and thrombosis within the actual areas of infarction, but vascular lesions are not found outside. Not all cases show vascular changes, so that it is difficult to attribute the cortical necrosis to a primary mechanical obstruction of the arteries. The pathogenesis of primary cortical necrosis remains a complete mystery.

Dr. Colby: Presumably toxic?

Dr. Mallory: A similar lesion has been produced in experimental animals with staphylococcus toxin, but in human beings there is rarely evidence of an infectious etiology. In this case the finger of suspicion points strongly to sulfonamide sensitivity. It is interesting, however, that no trace of persisting sulfonamide, either free or acetylated, could be found in the blood plasma.

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CASE 33182

Presentation of Case

A forty-three-year-old Jesuit brother entered the hospital because of midsternal pain during eating.

Fifteen years before entry the patient had begun to have midsternal pain that occurred during eating and was relieved when he ceased to eat. An x-ray film was taken at that time, and he was told that he had spasm of the esophagus. Subsequently, he began to have episodes of gaseous eructation and epigastric distress. Seven years later he had been put on a bland diet, which he had continued to follow ever since. Nevertheless, the symptoms continued essentially as before. In addition, he had intermittent bouts of diarrhea with left-sided and lower abdominal cramps. There had been no melena. Two months before entry the patient began to have difficulty in swallowing. When he tried to force food down he developed a severe pain in the right side of the chest. On two occasions he regurgitated undigested food. A month before entry he became unable to belch — such eructation had previously given him some relief. An x-ray film was stated to have revealed "a tumor" in the esophagus. The patient had lost 16 pounds during the year before entry, during which he had been making conscious efforts at weight reduction by means of dietary restrictions. The only other complaint was intermittent pain in the right knee radiating up and down the leg and occurring after protracted standing.

Physical examination revealed a well nourished, heavy-set man. A firm nodule, 0.5 cm. in diameter, was palpable in the left lobe of the thyroid gland, and there was a similar nodule just above the isthmus. Examination of the heart and lungs was negative. There was tenderness in the epigastrium just below the xiphoid but no spasm or palpable masses. The medial aspect of the right knee was slightly tender, but motion was normal.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 75 diastolic.

Examination of the blood showed a hemoglobin of 14.6 gm. and a white-cell count of 10,500, with 68 per cent neutrophils. The serum protein was 6.9 gm. and the nonprotein nitrogen 28 mg. per 100 cc., and the chloride 105 milliequiv. per liter. The urine was normal.

An x-ray film disclosed a round, soft-tissue mass between the heart and the dorsal spine, measuring about 8 cm. in diameter, that caused the barium to deviate toward the right and posteriorly and spread the esophageal lumen into a flattened, semicircular area (Fig. 1). The stomach and duodenum were outlined normally. The heart and lung fields were not remarkable.

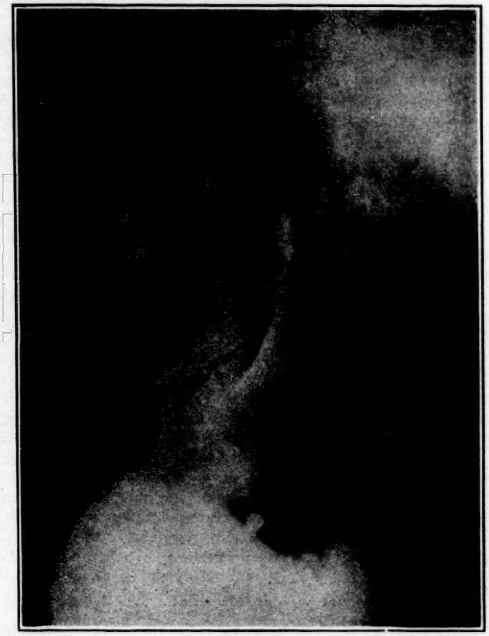

FIGURE 1.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LEROY SCHALL: This patient had a history of the development of midsternal pain during eating fifteen years previously, and a diagnosis of cardiospasm was made at that time. Was this pain really sharp pain or merely distress? Did it radiate to the back or to the shoulder? Was it relieved when he regurgitated food? Apparently it was. He had episodes of gastric eructations and had been on a bland diet for eight years. Apparently, he had not lost weight except when he tried to lose it. Two months before entry he had difficulty in swallowing. With this difficulty in swallowing he did not lose much weight, — only 16 pounds, — and on physical examination he was "a well nourished, heavy-set man." We believe that if a person has at least 5 mm. of esophageal lumen he can swallow well masticated food and that, so long as he can keep up fluid intake, he will not have too much weight loss.

Could the symptoms presented in this case have been due to carcinoma? At the age of forty-three years, they could. Yet pain is not an early symptom of carcinoma. If there is ulceration there may be pain on swallowing. There was no history of an esophagoscopy or biopsy. The x-ray report mentions a flattened esophageal lumen, and I take it that the lumen was also deviated. I do not believe that this was carcinoma of the esophagus because the symptoms were not present long enough. Pain is unusual, — except late in the course, — and there had not been sufficient weight loss.

There was a nodule in the thyroid gland. I do not know whether this is a red herring or not,

but could it have been a thoracic thyroid gland? I have not yet seen the x-ray films and do not know whether the obstruction was situated high or low, but the report says that there was a round mass behind the heart that had flattened the esophagus. I doubt whether this could have been a thoracic thyroid gland.

I do not believe that the patient had cardiospasm. In cardiospasm it is the lower end of the esophagus that is involved. He had distress and regurgitation of food, but there was no substernal pain. The x-ray film may show whether or not there was a real cardiospasm with dilatation of the esophagus above.

Could this have been a mediastinal cyst? I do not believe that it was a pulsion diverticulum, which generally involves the upper end of the esophagus and is most unusual in this area. Traction diverticulum is usually due to adhesions, perhaps from the vertebras, that pull the esophagus out. I rule out traction diverticulum of the esophagus in this area because it is usually higher.

Could this have been a new growth of the mediastinum? Dermoid tumors usually involve the anterior mediastinum. This growth was posterior, between the heart and the esophagus. Could something outside have caused pressure between the heart and the mediastinum?

There was no history of respiratory difficulty, so that, whatever the lesion, it was too low to cause pressure on the large bronchi. This area is too low for aneurysm. The mucosa appears intact, which is strong evidence against carcinoma. I shall therefore consider benign lesions of the mediastinum, among which are tuberculous lymphadenitis and Hodgkin's disease, although nothing in the history suggests tuberculosis. A gumma should also be considered, but I do not believe that it is likely.

The most probable diagnosis is a cyst of the mediastinum.

DR. CHESTER M. JONES: Would you include neurofibroma as a possible cause of the mass?

DR. SCHALL: I do not know. A neurofibroma may be a primary tumor of the mediastinum.

DR. JONES: This mass was posterior, and neurofibroma should undoubtedly be included.

DR. SCHALL: Yes; let us say that Hodgkin's disease, noninfectious lymphadenitis, tuberculous lymphadenitis and gumma are all possibilities, but I am in favor of a cyst.

DR. TRACY B. MALLORY: Is there anything further from the x-ray point of view?

DR. STANLEY WYMAN: As Dr. Schall has said, the mucosa is intact. The barium has been forced into a thin shell over the mass, and the deviation is more apparent to the right. The mass appears to arise outside the mucosa of the esophagus, which is not involved. The question is, Does it arise in the esophageal wall without arising in the mucosa?

DR. SCHALL: We must think of the myomatous group of tumors, if the mass arose from the wall. I do not believe that it was a lipoma, because that is pedunculated and is usually at the upper end extending down into the esophagus.

DR. W. WILSON SCHIER: Could a vascular tumor, such as cavernous hemangioma, have arisen there?

DR. RICHARD H. SWEET: I have seen only one such case. This was in a patient on whom I operated a few weeks ago. The tumor was in the superior mediastinum.

DR. MALLORY: Dr. Sweet, will you tell the findings at operation?

DR. SWEET: There were two reasons why we made a preliminary diagnosis of intramural benign esophageal tumor in this case — without the benefit of esophagoscopy, I might add. In the first place the x-ray appearance seemed to us, and I believe to Dr. Schatzki or whoever interpreted the films, to be characteristic of that type of tumor. The other reason was the nature of the symptoms. The patient really had to work hard to get anything through the esophagus. He had a good deal of discomfort, and a benign tumor or cystic tumor of the mediastinum of such relatively small size in my experience does not give dysphagia of the severity that he had or so much pain or discomfort. For these two reasons we thought that this was an intramural esophageal tumor.

The tumor lay toward the right. We exposed it on the left side of the chest and dissected it from behind the heart and from the right chest. We found that the longitudinal muscle fibers were spread out in such a way that groups of fibers were separated from one another, but by incising the muscularis, we could dissect it free. We broke into it and discovered that it was cystic. The mucosa was not involved. We were able to shell the cyst out of the wall of the esophagus and restored continuity by suturing the muscularis together.

CLINICAL DIAGNOSIS

Benign tumor of esophagus.

DR. SCHALL'S DIAGNOSIS

Cyst of mediastinum.

ANATOMICAL DIAGNOSIS

Congenital tracheobronchial cyst of esophageal wall.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Microscopically, sections of this cyst showed a considerable amount of inflammation and destruction of the lining epithelium over many areas, but in some spots ciliated columnar epithelium persisted, which established it as a congenital cyst of misplaced tracheobronchial epithelium. The location was not far from the spot where tracheobronchial fistulas are seen in early life.

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THE TAFT BILL

The Taft Bill (S. 545), which was introduced on February 10, 1947, is meeting with considerable approval and support from organized medicine. The Massachusetts Medical Society has endorsed many of the stated objectives of previously proposed national health legislation but has opposed revolutionary trends. It considers universal compulsory insurance undesirable and unnecessary, since the American public, physicians and governmental agencies are not ready for it. It believes that present progress is satisfactory and should be continued, instead of making a reckless leap into the realms of medical bureaucracy. Even if compulsory insurance eventually proves to be necessary, there should be an evolutionary change.

Organized medicine makes no claim that present medical care is adequate: it is still far short of meeting the needs of all the people. But the medical profession is trying to preserve values, and it appears that a good beginning has been made. Voluntary health insurance is rapidly expanding. The Blue Cross now has a membership approaching 30,000,000 in the Nation and about 2,000,000 in Massachusetts. The revised June contracts of the Massachusetts Blue Cross will provide comprehensive coverage of all hospital charges. The Massachusetts Blue Shield is also doing well, with a membership greater than 500,000. Rapid expansion is anticipated after the adoption of the revised June schedule, which will give complete surgical and obstetric care outside the hospital, as well as medical and surgical care in the hospital. To the few in the medical profession who have thus far failed to support this voluntary insurance program, it can only be pointed out that the definite trend toward one of two schools of thought — compulsory and voluntary — will eventually necessitate a decision to co-operate.

The Taft Bill aims to preserve and foster existing agencies and to ensure the continued independence of the American people and the medical profession. Briefly, it plans to bring together all the scattered federal health activities into a single national health agency, headed by an outstanding physician. It would provide grants-in-aid to states for the extension of medical care to people unable to pay for it, amounting to $200,000,000 a year for general surgical and medical services and to $20,000,000 a year for dental services, the states to match these grants-in-aid on a variable basis. It aims to encourage voluntary prepayment plans and to extend federal grants to pay the subscriptions of indigents, and it allows federal employees, through individual choice, to join voluntary health-insurance plans by payroll deductions. It would determine actual medical needs by requiring state surveys financed with federal subsidies, and it would provide grants-in-aid for research, especially in neuropsychiatry and dental health. It would also require states to have periodic medical and dental examinations of school children, if the parents cannot afford such services.

The objective of adequate medical care is to make it available to all the people regardless of financial status. Actually the Taft Bill is designed to reach, in particular, the low-income group. This is a special need. For those who can afford it, direct payment or coverage by a voluntary prepayment plan is the responsibility of the individual. The indigent group is now taken care of, after a fashion, by local welfare agencies or private charity. Subsidy from some tax source will probably be needed to provide unusual diagnostic costs and to meet the expenses of catastrophic illness in this group.

The attainment of adequate medical care for all the people should follow an evolutionary process over a long period, with co-operation of all concerned. The Taft Bill seems to be, at least so far, the best framework on which to build the kind of health legislation that the country needs. It is to be hoped that, after conflicting groups have made the necessary compromises that are a proper mechanism for forging laws in a democracy, the foundation of a broad progressive system of medical care will be evolved. In the meantime, this bill warrants the attention and study of every physician who is interested in his own future, the future of organized medicine and the health of the people of the United States.

MAY DAY — CHILD HEALTH DAY

May Day, since a Congressional resolution was passed in 1928, has been traditionally Child Health Day. This year its observance is taking a slightly different form than usual. In a world over-ready for tranquillity but overaccustomed to violence, the current May Day will call attention to the fact that accident, not disease, is now the leading cause of death among children. In the interest of accident prevention in the home, the Children's Bureau set aside the week of April 27 in which to conduct a nationwide educational campaign.

Accidents, according to available statistics, now annually take the lives of nearly twenty thousand boys and girls under twenty years of age, and many more thousands are injured and crippled. Most of these accidents are preventable. In 1944, six thousand children under five years of age died from injuries sustained at home. Of these, two thousand died of burns, and thirteen hundred as a result of mechanical suffocation. Human carelessness, as a killer, is taking the place of pneumonia, enteritis, measles, diphtheria, meningitis, poliomyelitis, whooping cough and scarlet fever combined; many of these diseases, as a result of human intelligence effectively applied, are losing much of their terror.

Nothing can be done about the lives that have been lost from accident except to make their numbers stand as a grim reminder of the carelessness with which we live, and a warning that we must devote ourselves to attaining a better record for the future. Much can be done for the uncounted thousands who have survived their injuries and still live on as more or less permanent cripples.

Many of these patients are treated under the federal-state crippled children's program, administered by the states and financed largely with federal funds, and more would be cared for if those who need the help could be found. This seems to be one of the present problems, — to find the patient, — since the family frequently does not know of the aid that can be obtained without charge and without regard to financial circumstances.

The fact that accidents are now the leading cause of death among children does not mean that the death rate from accidents has actually risen. What it does mean is that science has been able to effect a decline in the death rate from disease. That decline has not been paralleled in accident prevention by the use of ordinary common sense and an acceptance of responsibility for the welfare of those who still require protection and guidance.

MICHAEL ALOYSIUS TIGHE

1882–1947

Michael Aloysius Tighe was born at Meriden, Connecticut, and moved to Lowell at an early age. He was a graduate of St. Patrick's Boys' School and attended St. Francis Preparatory School in Brooklyn, New York. After graduating from Boston College, where he received an A.B. degree in 1903, he entered Harvard Medical School, receiving his M.D. degree in 1908. He soon established himself in practice in Lowell and was immediately appointed to the surgical staff of St. John's Hospital, where he served for nearly forty years, being chief of the surgical staff at the time of his death. His faithful service to his patients and to the hospital can never be adequately measured.

For a number of years he held the office of city physician and was at one time associate medical examiner for the Northern Middlesex District. He had been president of the Middlesex North District Medical Society.

Early in his medical career Dr. Tighe became a councilor of the Massachusetts Medical Society. His experience on matters of general medical and public concern began about the time the Workmen's Compensation Act was passed in 1912. He believed that the Act should be amended for the general good. He visited various district societies and presented his arguments in a convincing manner and later appeared before the Legislature. The Act was amended and has since proved to be a most satisfactory piece of legislation. Subsequently he was an important figure in questions of public relations, and his opinions were eagerly sought by laymen and members of the profession. He had an uncanny sense of seeing through debatable points quickly and was able to clarify muddled discussions in the form of a motion clearly and briefly stated. He was always an important member of a committee, but he never assumed a leading role unless his opinion was fortified with plainly stated facts and sound logic.

Because of his wide knowledge of subjects pertaining to the Society, he was appointed secretary in 1941, a position that he filled capably for nearly six years. Through his faithful, diligent and efficient work he will undoubtedly be recognized as one of the outstanding secretaries of the Society, and he will always be remembered as the "war secretary." Only a man of high ideals and fine motives could have carried on so successfully through those many troublesome years and have still been held in such great esteem and respect. In addition, he believed that the Society should render more service to its fellows, and for that reason gave much needed aid and sympathetic advice to returning veterans and new members. It was largely through his rapt devotion to his secretarial duties that he won the real affection and friendship of all members of the Society.

His clear thinking was made evident by the excellent manner in which he expressed himself, his enunciation showing care and forethought. By nature he combined gentleness with sensitiveness. He was appreciative of the finer things in life. He stood for justice and fairness, and he insisted on the truth as he saw it. In heated arguments he kept his dignity and poise and never created animosity. Indeed, he was a cultured and scholarly gentleman.

He had traveled considerably both in this country and abroad. Besides enjoying prose and poetry, he derived a great deal of pleasure from golf — not only for the game itself but also for the companionship that it afforded. He adored his family, and the evening before his death, all members gathered at his home for the celebration of his birthday.

Dr. Tighe was a fellow of the American College of Surgeons, American Medical Association and New England Obstetrical and Gynecological Society and a member of the Harvard Club of Boston and Longmeadow Golf Club of Lowell.

He is survived by his widow, three sons, a daughter, five grandchildren and two sisters.

Impressive rites for Dr. Tighe were held at the Church of the Immaculate Conception in Lowell. The extremely large attendance by physicians from all parts of the Commonwealth, nurses, hospital executives, friends and former patients attests the high regard in which he was held.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

ANNUAL GOLF TOURNAMENT

The annual golf tournament of the Massachusetts Medical Society will be held at the Woodland Golf Club, 1897 Washington Street, Newton, commencing at 1:00 p.m. on Tuesday, May 20. Prizes for low gross and net scores will be awarded, as well as the Burrage Bowl, emblematic of the championship of the Society.

Dr. Henry W. Godfrey has been appointed chairman of the Golf Committee, and entries should be sent to him at 14 Hancock Street, Newton. Post entries are allowed.

There will be an opportunity to have dinner at the club for those who desire it.

SIDNEY C. WIGGIN, *Chairman*
Committee on Arrangements

DEATHS

PERKINS — George E. Perkins, M.D., of Belmont, died April 3. He was in his seventieth year.

Dr. Perkins received his degree from Georgia College of Eclectic Medicine and Surgery in 1913. He was a fellow of the American Medical Association. He was a member of the staffs of the Boston Dispensary and the Massachusetts Memorial Hospitals and was acting director of the Division of Venereal Diseases, Massachusetts Department of Public Health.

His widow survives.

STONE — Henry E. Stone, M.D., of Boston, died March 31. He was in his fifty-sixth year.

Dr. Stone received his degree from Tufts College Medical School in 1912.

His widow and a son, Dr. Nathaniel M. Stone, survive.

A HUNDRED YEARS AGO

As they threatened, the Physicians of Berkshire County have petitioned the Great and General Court of Massachusetts for new legislation concerning the Massachusetts Medical Society. At present, they claim, its meetings, its funds and its library are confined in Boston, at the eastern extremity of the Commonwealth so that the portion of the profession residing in the *opposite extremity* can derive little or no benefit from either. They ask that the State Medical Society may be so re-organized that a participation of the funds and library already accumulated may be secured to County Medical Societies or that the County of Berkshire may be constituted a separate and distinct medical society, clothed with the usual powers and privileges pertaining to such bodies. — The Counsellors of the Massachusetts Medical Society deprecate this action. It can be shown, they say, that more property has been given by the parent Society to the County of Berkshire than the whole amount of assessments ever received by the Society from them. The library of the Society is a small collection of old books, the result entirely of donations and legacies. It is but little used in Boston, and by a regulation of the Society, any District Society may carry off sixty volumes at a time for the use of its members. Of this privilege the County of Berkshire has freely availed itself. If by "the usual powers and privileges" of medical corporations, it is intended to include the power of conferring *licenses to practice physic*, this power becomes dangerous and liable to abuse. If such a power is granted to the physicians of Berkshire, there is no reason why the physicians of any other county in the Commonwealth may not claim the like privilege. And thus the State might be cut up into small and irresponsible tribunals, disposing of licenses for a pecuniary compensation, and not accounting to any higher authority for abuse — which might result from the misuse of their privileges. — An exhibition of extraordinary interest to humanity occurred at the Massachusetts General Hospital on Saturday last. A patient was presented who, we understand, was laboring under paraplegia, having its origin in a caries of the lower dorsal vertebra, and for which Dr. Warren proposed the actual cautery. After the patient had inhaled the letheon, Dr. Warren run an iron rod, heated to a white heat, to the length of about two feet, up and down the back, each side of the spine, burning two lines on one side and one on the other, and then carried it zigzag across, between the spinous processes, the same distance. The patient during this process was wholly unconscious of pain, under the severest test to which he could be subjected — that of a hot iron applied to the naked skin. — Dr. Ames of Wayland, Mass., in forty-one operations drew from a lady in that town, who died not long since, *fourteen hundred pounds of water!* On one or two occasions two pailsful of fluid were taken away at the same time. The lady, immediately after each operation, till towards the close of life, was so completely relieved that she at once assumed the management of her domestic duties. There may have been more remarkable cases on medical record, but nothing, we believe, more striking has occurred in this region. — A young native of Chester, Vt., J. H., 19 years old, who is maintained chiefly by the benevolent contributions of medical gentlemen, on whom he calls while travelling over the country, exhibits in his person, one of the most extraordinary and inconvenient malformations imaginable. In the first place there is only a portion of a bladder, about the size of a hen's egg, and that inverted — and instead of being within the cavity of the abdomen, it

is outside. The ureters do not enter the bladder at all, but make their exit above the brim of the pelvis on either side. The glans is all that indicates the existence of the penis, and projects out from the place where nature intended that organ should be located. An opinion has been given that the bones are not united in the usual manner in front, but are tied imperfectly together by the intervention of a ligamentous band. It strikes us that an effort should be made to lessen this poor wandering boy's sad calamity. If some benevolent gentleman would give him the use of a free bed awhile at the Massachusetts General Hospital,* our unbounded confidence in the ingenuity and skill of the surgeons of that institution, leads us to believe that he might there find at least some relief. — Tuesday, 3rd inst., being the concluding day of the courses, Dr. Warren gave his last lecture to the Medical School. He took leave of his audience, by wishing for his students a continued zeal in the prosecution of their studies; for the candidates for graduation a triumphant passage through the narrow gate that leads to professional honors; and for the young practitioners abundant opportunities of relieving the poor and, adequate reward of their labors from the rich, and, above all, a conscientious discharge of their duties through life. — At the meeting after the close of the exercises, Dr. C. T. Jackson was called upon by Dr. Bigelow to speak in regard to the insensibility to pain produced by inhalation of sulphuric ether vapor. Dr. Jackson would only re-assert that he discovered that insensibility to pain was produced by such inhalations and that he communicated the fact to one of his pupils in February, 1846, and requested him to try the experiment when he had a tooth extracted. He regretted that any misunderstanding should have arisen concerning the discovery. He was willing to allow great credit to others for their enterprise and zeal in promoting its introduction, and for skill in improving his originally simple apparatus. Yet it would certainly be unwarrantable for the miner, who carried Davy's safety lamp into the fire damps of a mine, to dispute the claims of its original inventor; for he received that instrument already proved to be efficient, with the assurance that it would guide him in safety amid the explosive gases of the mine. — Extracted from the *Boston Medical and Surgical Journal*, March, 1847.

R. F.

*The records of the Massachusetts General Hospital reveal that in January, 1846, J. H., nineteen years old, was admitted to the Surgical Service for congenital malformation of the urinary organs and was discharged unrelieved.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SMALLPOX PROGRAM FOR MASSACHUSETTS

The appearance of 8 cases of smallpox in New York City recently, with a total of 2 deaths, has given rise to considerable and unwarranted concern. The fear that this disease may attain even larger epidemic proportions has been recently aggravated by the misinterpretation of a radio report of a smallpox outbreak within an institution.

There has been no reported case of smallpox within Massachusetts for the past fifteen years. In the event of the occurrence of this disease within Massachusetts, a program has been formulated for the care and treatment of such cases. If the diagnosis of smallpox is suspected in any one case, it is imperative that the state or local health department be notified immediately.

The Biologic Laboratory of the Massachusetts Department of Public Health has on hand sufficient vaccine to satisfy requests at a normal demand level. Personnel from other divisions of the Department of Public Health is being diverted to assist in the present work of increasing the present supply of smallpox vaccine. Physicians are cautioned, however, that in the event of a panic concerning the New York epidemic, the demand for vaccine will far exceed the supply.

To clarify the status of smallpox in Massachusetts, a conference of public-health officials representing the Massachusetts Department of Public Health and the Boston Health Department was called, and the following recommendations were adopted:

No mass vaccination of the general public is indicated.
Priority for use of the present supply of vaccine shall be restricted in the following order:

(*a*) To actual contacts of cases.
(*b*) To physicians, nurses and hospital personnel.
(*c*) To unvaccinated persons traveling to areas of smallpox prevalence.
(*d*) To infants six to twelve months of age and for revaccination of preschool children prior to entering school.

The above information has been forwarded to all hospitals, medical societies and boards of health within the Commonwealth.

DIAGNOSTIC TESTS FOR CERTAIN VIRUS DISEASES

For the present the Department has available, through a co-operative arrangement with Harvard Medical School, facilities for making a limited number of serologic tests for Influenza A and B by the red-cell agglutination inhibition technic, for mumps, psittacosis and lymphogranuloma venereum by complement-fixation tests and for lymphocytic choriomeningitis by neutralization tests.

Specimens should be submitted in the Department's special outfit and accompanied by properly filled out forms entitled "Request for Serological Tests for Certain Virus Diseases." The special outfit to be used, which is the same as the Department's undulant-fever outfit, and the special forms to be filled out may be obtained from local boards

of health or directly from the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30.

In each suspected case, two aseptically collected 4-cc. serum specimens are required, the first taken as soon as possible after the onset of the disease, and the second ten to fourteen days later (four to five weeks later in cases of lymphocytic choriomeningitis). If facilities for separation of serum are not available, 10 cc. of clotted blood for each specimen may be substituted if it is mailed to the laboratory at once. *Since positive diagnosis can be made only if a rise in antibody titer is demonstrated during the course of the illness, two specimens must be sent.* Tests for diagnosis, therefore, will be run only on paired specimens. If information regarding past mumps infection and consequent immunity alone is desired, however, only one specimen need be submitted.

For information regarding serologic diagnosis of other virus infections, the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30 (telephone, ARNold 5440), should be consulted directly.

It should be noted that none of these tests will assist in the confirmation of a diagnosis during the early acute stage. They are useful mainly in making a diagnosis in retrospect.

If intelligent selection is exercised by physicians in sending in specimens, this service may be made permanent by the Department. Because funds are limited for reimbursing Harvard Medical School for the tests, the service will have to be discontinued if lack of selection results in too large a volume of tests.

NEW APPOINTMENTS

Mary E. Spencer, Ph.D., nationally known health educator and author of several books, has been appointed chief of the Bureau of Health Information of the Massachusetts Department of Public Health. Dr. Spencer is well known in Washington circles for her work as director of the Health Education Bureau of the National Welfare Conference, in which position she represented the United States at the World Federation of Education Association at Geneva. She also served on the Hoover White House Conference on Child Health and Protection. Prior to her appointment, Dr. Spencer held the position of director of health education in the schools of Malden. She is professor of public health at Wellesley College Graduate School of Hygiene. She is vice president of the Massachusetts Public Health Association, chairman of health and nutrition of the American Association for Health, Physical Education and Recreation and a former president of the New England Health Education Association. She is the author of the textbooks *Health Education for Teachers* and *Health Through the School Day*, as well as numerous professional articles.

Eugene R. Sullivan, M.D., has been appointed assistant director in the Division of Biologic Laboratories, Massachusetts Department of Public Health. Dr. Sullivan, recently a lieutenant colonel in the Army Medical Corps, served three years overseas as chief of laboratories, Sixth General Hospital, consultant on blood and blood transfusions for the North African and Mediterranean theaters of operations and a member of a board for the study of the treatment of the seriously wounded. Prior to his Army service, Dr. Sullivan held positions at Harvard Medical School, Massachusetts General Hospital and Michigan University School of Public Health, working in the fields of internal medicine, infectious disease and laboratory sciences.

Martha Howard Fales, B.A., formerly dental health consultant, Michigan Department of Health, has joined the staff of the Massachusetts Department of Public Health, Division of Dental Health, as public-health dental-hygiene supervisor.

Julian M. Karasoff, D.V.M., has been appointed veterinary food inspector in the Division of Food and Drugs, Massachusetts Department of Public Health. Prior to his appointment, Dr. Karasoff practiced privately as a veterinary. He also served as slaughtering inspector in Waltham.

Salvatore R. Traina, M.D., formerly command surgeon, Seventh Air Service Area Command in Tokyo, is now serving as physician in charge of the mobile unit of the State Blood Donor Program, Division of Biologic Laboratories, Massachusetts Department of Public Health. Prior to his appointment, Dr. Traina served for twenty-eight months in the Asiatic-Pacific Theater, being discharged with the rank of major in the Medical Corps. He is a diplomate of the National Board of Medical Examiners.

Barbara Ford Carter, M.D., has been appointed assistant district health officer of the North Metropolitan District, Massachusetts Department of Public Health. Dr. Carter was formerly house officer and assistant resident, Third Medical Service, Boston City Hospital.

BOOK REVIEWS

Fees and Fee Bills: Some economic aspects of medical practice in nineteenth century America. By George Rosen, M.D., Ph.D. 4°, paper, 91 pp. Baltimore: Johns Hopkins Press, 1946. $1.50.

Dr. Rosen in this monograph has made a valuable contribution to the medical economic history of the United States. He has published a number of fee tables from various sections of the country and has shown the gradual changes of professional fees from 1815 to 1891. The fee bill of the Boston Medical Association of 1864 is reproduced from the *Boston Medical and Surgical Journal* of the same year.

It is not generally known that the Boston Medical Association was established for the sole purpose of regulating the fees of physicians and the ethics of the profession. It was formed in 1806 and became extinct in 1910. It published from time to time, beginning in 1808, fee tables and a pamphlet called *Medical Police*, in which ethics and fees were discussed. Its records are now in the Boston Medical Library.

This monograph loses some of its value because of the lack of an index. At least a list of the fee tables should have been published. It should find a place in all medical-history collections, however, as well as in business libraries.

Women in Industry: Their health and efficiency. By Anna M. Baetjer, Sc.D. Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research, National Research Council. Prepared in the Army Industrial Hygiene Laboratory. 8°, cloth, 344 pp., with 122 tables. Philadelphia and London: W. B. Saunders Company, 1946.

This study was made during World War II for the purpose of ascertaining the utilization of womanpower in industry to further the war effort. An exhaustive critical review was made of the literature to determine whether such utilization had a sound physiologic basis. The material is well documented with graphs and statistical tables. The text is divided into main sections, comprising seventeen chapters, and four appendixes, as well as a bibliography of twenty-two pages. The sections deal with the following aspects of the subject: the physique of women in relation to work, fatigue and physical stress, absenteeism due to sickness, accidental injuries, occupational diseases, gynecologic and obstetric problems and mortality and fertility in relation to occupation.

This monograph presents information about the ability of women to perform operations previously considered suitable for men only and also gives a clear picture of the facts known about the relation of employment to the health of women. It is not the intention to justify the employment of women in industry but to make available valuable information for the proper job placement of women when their service is required. The study endeavors to present the scientific facts known concerning the health and efficiency of women in relation to their employment on the basis of the literature and the information gained during the war, and to indicate phases of the problem requiring further investigation, to obtain maximum health and working efficiency. Section seven is devoted to a summary and lengthy conclusions in which each main section is treated separately and all pertinent facts relative to each are analyzed. The appendixes comprise valuable collateral information, including a table showing the distribution of gainfully employed women according to occupational classes and industrial groups as shown by the 1940 United States Census, a list of occupations suitable for women and a summary of state labor laws for women as of 1944. In addition to the main bibliography, selected references are appended to each chapter.

The material is well organized, and the text well printed on good paper. This monograph should be in all medical libraries and should prove valuable to all industrial physicians.

Water Treatment and Purification. By William J. Ryan, M.E. Second edition. 8°, cloth, 270 pp., with 66 illustrations. New York and London: McGraw-Hill Book Company, Incorporated, 1946. $2.75.

This manual, first published in 1937, has been revised to include descriptions of processes that have come into use since the issue of the first edition. These include organic ion exchange, materials for water softening, acid absorbents, demineralization, the treatment of boiler water to prevent embrittlement, new equipment for accelerating the lime-and-soda ash softening process, new developments in the use of chlorine for sterilization and the stabilization of water to prevent scale deposits.

Although this manual has been written primarily for engineers and others concerned with water purification, it should prove useful to all persons interested in pure water and water supply. The chapters on impurities, sedimentation and coagulation, filtration and water analysis are of public-health interest. The material is well organized, well written and printed with a good readable type on good paper. The manual is recommended for reference purposes.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Three Unpublished Drawings of the Anatomy of the Human Ear. By the late Max Brödel, with the assistance of P. D. Malone, Stacy R. Guild and S. J. Crowe. 4°, cloth, 9 pp., with 4 illustrations and frontispiece. Philadelphia: W. B. Saunders Company, 1946. No charge.

Max Brödel, 1870–1941, pioneer medical artist, long connected with the Johns Hopkins University School of Medicine, is honored in this publication by the W. B. Saunders Company. These unpublished drawings are excellent examples of the high quality of work executed by Brödel, and are thoroughly characteristic of his style. They are presented to the medical profession as a tribute to the memory of a great artist in his chosen field.

The Normal Encephalogram. By Leo M. Davidoff, M.D., professor of clinical neurological surgery, Columbia University College of Physicians and Surgeons, and attending neurologic surgeon, Montefiore Hospital, New York City; and Cornelius G. Dyke, M.D. Second edition, thoroughly revised. 8°, cloth, 232 pp., with 155 illustrations. Philadelphia: Lea and Febiger, 1946. $5.50.

This second edition of a standard monograph has been revised on the basis of an accumulation of over eight thousand encephalograms, more than double the number available for the first edition. The text is well printed with a good type, and the illustrations are excellent. The book is recommended to all medical libraries and to neurologists and physicians interested in the subject.

Exercises in Electrocardiographic Interpretation. By Louis N. Katz, M.D., director of cardiovascular research, Michael Reese Hospital, Chicago, and professorial lecturer in physiology, University of Chicago School of Medicine. Second edition, thoroughly revised. 4°, cloth, 288 pp., with 141 illustrations. Philadelphia: Lea and Febiger, 1946. $6.00.

This manual, a companion volume to the author's large work on the same subject, has been revised to conform to the advances in electrocardiography. The total number of cases has been increased to one hundred, and thirty-eight have been discarded and new ones substituted. The descriptions and interpretations of the other cases have been revised to conform to the newer terminology of the subject. The work is written for persons requiring practice in reading unknown electrocardiograms. The book is well published in every way and should prove valuable to students of the subject.

Clinical Electrocardiography. By David Scherf, M.D., associate professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals; and Linn J. Boyd, M.D., professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals. Second edition. 4°, cloth, 267 pp., with 243 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $8.00.

This second edition of a standard work has been thoroughly revised by the addition of new material. Some sections have been completely revised, whereas others have been expanded. Extensive bibliographies are appended to each part. The text is well printed in a two-column format.

Urologic Roentgenology. By Miley B. Wesson, M.D. Second edition, thoroughly revised. 8°, cloth, 259 pp., with 258 illustrations. Philadelphia: Lea and Febiger, 1946. $5.50.

In this new edition of a standard work, the text has been practically rewritten, and the literature brought up to date. Many of the illustrations have been deleted, and new ones substituted. The purpose of the book is to provide a manual for beginners in the field of urography. The first chapter furnishes a short history of the subject. The material is well organized, and the text is well printed with a good readable type. The book should prove useful to physicians interested in the subject.

A Primer for Diabetic Patients: An outline of treatment for diabetes with diet, insulin and protamine-zinc insulin, including directions and charts for the use of physicians in planning diet prescriptions. By Russell M. Wilder, M.D., Ph.D., professor and chief, Department of Medicine, Mayo Foundation, University of Minnesota, and senior consultant, Division of Medicine, Mayo Clinic. Eighth edition, reset. 18° cloth, 192 pp., with 8 illustrations. Philadelphia and London: W. B. Saunders Company, 1946. $1.75.

This standard manual for diabetic patients, first published in 1921, has been slightly revised to conform to minor

changes in procedure developed since 1941, the date of the seventh edition. The text is written in a practical, nontheoretical manner and is based on the instruction given in the Diabetic School at the Mayo Clinic and on thousands of cases. The material is well organized and well written in plain language. The topics covered include urine testing, administration of insulin, complications, including gangrene, diet and foods.

Wm. Beaumont's Formative Years: Two early notebooks, 1811-1821. With annotations and an introductory essay by Genevieve Miller, M.A., Institute of the History of Medicine, Johns Hopkins University. 8°, cloth, 87 pp., with 21 illustrations. New York: Henry Schuman, 1946. $6.00.

Miss Miller has written an interesting introduction and has provided copious explanatory notes to this reproduction of the two notebooks of Beaumont — one medical and the other general — owned by the Washington University School of Medicine, St. Louis. The first notebook contains excerpts from medical authors, case histories, prescriptions and notes on military medicine. The second contains literary excerpts, including poetry, and war and travel diaries. The book is a credit to the publisher. It is beautiful in conception and should be in all medical libraries and medical-history collections.

New Aspects of John and William Hunter. I. Everard Home and the Destruction of the John Hunter Manuscripts. II. William Hunter and His Contemporaries. By Jane M. Oppenheimer, Bryn Mawr College. With a foreword by Fenwick Beekman, M.D. 8°, cloth, 188 pp. New York: Henry Schuman, 1946. $6.00.

In these studies Miss Oppenheimer has made a valuable contribution to medical history. In Part I she made a new investigation and a reinterpretation of the destruction of John Hunter's manuscripts by his brother-in-law, Sir Everard Home, based on an analysis of the personal relations existing between Home, Hunter and William Clift. Part II is devoted to an evaluation of the personality of William Hunter, the great obstetrician, as revealed by his friendships with outstanding personages of his time. Likewise, the author discusses his disputes with his famous brother John. Copious notes and bibliographies are appended to both parts. The book is recommended for all medical-history collections.

Parergon Supplement. By Mead Johnson and Company. 8°, paper, 33 pp. Evansville, Indiana: Mead Johnson and Company, 1946. Sent on request.

This pamphlet is a bibliography of art technics in various mediums especially selected for the physician artist. In addition there are a number of short papers written for the beginner by the officers of the American Physicians' Art Association. The material should prove valuable to all physicians interested in the various aspects of art.

NOTICES

REUNION AT SPRINGFIELD HOSPITAL

A combined reunion of former interns and graduates of the nursing school will be held at the Springfield Hospital on Saturday, May 17. The program will consist of operations and clinics by the medical staff and demonstrations and talks in the classrooms of the Nurses' Residence by the nursing department in the morning. At noon the unveiling of the World War II Memorial will take place in the main lobby of the hospital, following which luncheon will be served in the cafeteria to all the hospital group. The afternoon will be free for visiting and a tea in the living room of the Nurses' Residence, and the reunion dinner will be held at the Hotel Kimball at 7:00 p.m.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fortieth anniversary meeting and dinner of the Massachusetts Society of Examining Physicians will be held on Wednesday, May 7, at 6:30 p.m., in the State Suite of the Copley-Plaza Hotel, Boston. Dr. James C. White, chief of the Neurosurgical Service, Massachusetts General Hospital, will be the guest speaker and present a paper, illustrated by lantern slides, on the topic "The Contributions of Neurosurgery to Problems of Vascular Disease and Visceral Pain." Members of the Society will participate in the discussion, which will be opened by Dr. Charles A. Robinson. Reservations for the dinner may be made with the assistant secretary, Miss Anne Rodman, 157 Fourth Street, Medford, Massachusetts.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, May 7 — Heparin Therapy of Thromboembolic Disease. Dr. Arnold Starr.
Friday, May 9 — Methemoglobinemia and Sulfhemoglobinemia. Dr. C. A. Finch.
Wednesday, May 14 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, May 16 — The Control of Ascitic-Fluid Formation in Hepatic Cirrhosis by Albumin; Mechanisms of Albumin Action in Water and Sodium Balance of Other Diseases. Dr. S. Howard Armstrong.
Wednesday, May 21 — Porphyrins. Dr. Marvin Bloom.
Friday, May 23 — The Systemic Manifestations of Rheumatoid Arthritis. Dr. Walter Bauer.
Wednesday, May 28 — Clinicopathological Conference. Drs. Richard Chute and H. E. MacMahon.
Friday, May 30 — Holiday.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 8

FRIDAY, MAY 9
*9:00–10:00 a.m. Methemoglobinemia and Sulfhemoglobinemia. Dr. C. A. Finch. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, MAY 12
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 13
12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 14
*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

APRIL 26–MAY 4. Industrial Health Meetings. Page 456, issue of March 20.
MAY 6. Greater Boston Medical Society. Page 610, issue of April 17.
MAY 7. Massachusetts Society of Examining Physicians. Notice above.
MAY 7–28. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.
MAY 8. Cerebral Hemorrhage. Dr. Raymond Adams. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
MAY 9. Boston University School of Medicine Alumni Association. Page 554, issue of April 10.
MAY 9. Tuberculosis Institute. Page 646, issue of April 24.
MAY 12. Phi Delta Epsilon Lecture. Page 646, issue of April 24.
MAY 17. Reunion at Springfield Hospital. Notice above.
MAY 19–22. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
MAY 20–22. Massachusetts Physicians' Art Association. Page 340, issue of February 27.
JUNE 5–8. American College of Chest Physicians. Page 418, issue of March 13.
JUNE 7 AND 8. American Society for the Study of Sterility. Page 304, issue of February 20.

(Notices continued on page xix)